DO CANINES EXPERIENCE THE EFFECTS OF HEART RATE TURBULENCE?

A Thesis

presented to

the Faculty of California Polytechnic State University,

San Luis Obispo

In Partial Fulfillment

of the Requirements for the Degree

Master of Science in Engineering, with Specializations in Biomedical Engineering

by

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June, 2009

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ABSTRACT

Do Canines Experience the Effects of Heart Rate Turbulence?

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Background

The canine cardiac system has been the model against which many Class III cardiac devices are validated. Thus, it is expected that the canine heart has very similar electrical model to that found in humans. In 1999, the absence of Heart Rate Turbulence (HRT) after a single Pre-Ventricular Contraction (PVC) was linked to high-risk patient after acute myocardial infarction. Studies of HRT were performed on high-risk patients with Holter-Monitors as were most subsequent HRT studies. If HRT could potentially be used as a risk factor of heart disease, it is interesting to study whether HRT is present following a PVC in otherwise healthy canines.

Methods

For multiple months, five non-medicated, healthy canines were chronically monitored from between 1 and 8 sessions each. At each session, the canines were ventricularly paced to induce PVCs. Electrical signals, as seen through both a right-ventricular lead and Electrocardiogram (ECG) signals, were captured and analyzed to determine whether the canines displayed HRT following each induced PVC. As a contrasting data set, for the majority of the canines, data was also collected once the canines were sedated.

Results

HRT was noted in all non-medicated and healthy canines. Of the two factors of HRT (slope and onset), TS was the most prominent indicator of HRT. In each canine, the slope was far greater

than the 2.5 ms per RR interval threshold varying from 9.8 to 68.8 ms per RR interval. The onset was marked as HRT (onset less than 0%) in 22 of the 26 session.

Additional data was analyzed for healthy yet medicated canines showed that sedation affected HRT, but that HRT was generally noted.

Conclusion

The canine model displayed a similar HRT characteristic as humans during normal and parasympathetic inhibited states. The presence of HRT in canines is most reliable when using TS. Further study in this area with naturally occurring PVCs would be of interest.

Preface

The work presented in this thesis was an independent research project in the interest of St. Jude Medical for the Cardiac Rhythm Management (CRMD) Research Department. Dr. Taraneh G Farazi, Director of Research, CRMD championed the idea and facilitated the means to collect data. Dr Farazi met with me periodically to discuss my findings and to guide me.

The study protocol was executed as an extension of an existing study being performed by Yelena Nabutovsky, who was in the role of Senior Staff Scientist, CRMD. The HRT research did not require a change to either the equipment or implant setup, so I created an addendum to Ms Nabutovsky's study protocol, as seen in Appendix A, which was required to be approved by the animal lab before conducting the study. Once the protocol was approved, I attended the first data collection session and ran the protocol. After that point, Ms Nabutovsky conducted the following data collection dates on my behalf. Ms Nabutovsky also provided drafts of the Matlab functions which served as the basis for the data analysis tools used in this study.

The advice, guidance and knowledge of both Dr Farazi and Ms Nabutovsky were paramount in the success of this research paper.

Table of Contents

List of Tables ix
List of Figures x
1. Introduction 1
2. Background 3
2.1. Canine in Medical Research 3
2.2. Sympathetic versus Parasympathetic 3
2.3. Cardiac Electrical Signal 4
2.4. Heart Rate Turbulence terminology 6
3. Review of the Literature 7
3.1. Heart Rate Turbulence 7
3.2. Heart Rate Turbulence Quantifiers 8
3.2.1. Turbulence Onset 8
3.2.2. Turbulence Slope 9
3.3. Original HRT Data Samples 9
3.4. Subsequent HRT Studies 10
4. Materials and Methods 14
4.1. Study Criteria 14
4.1.1. Subject-Related Requirements 14
4.1.2. Data-related requirements 15
4.2. Study Design and Population 15
4.2.1. Parent Study 15
4.2.2. Sample size 16
4.3. Physical Setup 17
4.3.1. Subject-related equipment 17
4.3.2. External equipment 18
4.3.3. *Data Analysis Equipment* 18
4.4. Data Collection 20
4.4.1. Electrical Data 20
4.4.2. Data Acquisition 20
4.4.3. *Protocol* 20
4.4.4. *Follow-up* 21
4.5. Data Analysis 21
4.5.1. Overview 21
4.5.2. Procedure Inputs 22
4.5.3. Trims 22
4.5.4. Procedure 26
4.5.5. Procedure Outputs 30
4.5.6. Software Tools - General 31
4.5.7. Software Tools - Definition 31
4.5.8. Statistics 36
5. Results 38
5.1. Trims used 38
5.2. HRT data collection session data 39

5.3. HRT data summary 40
5.4. Classification 41
6. Discussion 43
6.1. Sedation 43
6.2. Study challenges 43
6.3. Study limitations 46
6.3.1. Data collection 46
6.3.2. Data analysis 47
6.4. Potential uses 49
6.5. Future Research 50
7. Conclusion 52
Bibliography 54
Appendix A – Study Plan 56
Appendix B – Parent Study Plan 60
Appendix C – Data Analysis Software 63
Appendix D – Raw Data Analysis Results 75

List of Tables

Table 1 Trims used for valid analysis of HRT data 39
Table 2 Final summary of averaged data collection sessions 41
Table 3 Final Analysis Results 42

List of Figures

Figure 1 Annotated example of a segment of a normal electrocardiogram 5
Figure 2 Einthoven's Triangle 5
Figure 3 Electrocardiogram with annotation of HRT specific terminology 6
Figure 4 Turbulence Onset Diagram..... 9
Figure 5 Turbulence Slope Diagram..... 9
Figure 6 St Jude Medical Epic HF Header assembly with trancutaneous connector 17
Figure 7 Equipment layout for study 19
Figure 8 Correctly annotated data sample file (x-axis is time in seconds, y-axis is amplitude)... 27
Figure 9 Incorrectly annotated data sample files – Wrong PVC 29
Figure 10 Incorrectly annotated data sample files - Over-sensing 30
Figure 11 Plot of averaged data for *Canine Five* dated 01/04/2005..... 40
Figure 12 Losing a beat following the PVC 46
Figure 13 Mean Heart-Rate Data (non-medicated) 52

1. Introduction

A Premature Ventricular Contraction (PVC) also referred to as a Ventricular Premature Beat (VPB) or extrasystole, is a form of irregular heartbeat in which the ventricle contracts before the chambers are refilled completely. This results in a "skipped beat" followed by a stronger beat.[1] The known causes of PVCs can vary and do not directly correlate to heart disease. Besides heart disease, there are multiple non-physiological factors such as caffeine, alcohol, tobacco and certain prescription drugs that can induce PVCs.

There is a phenomenon in humans where the cardiac system compensates for the missed beat of a PVC by temporarily speeding up the heart rate. This phenomenon is known as Heart Rate Turbulence. HRT is described as:

> …the return to equilibrium of heart rate after a premature ventricular contraction. It consists of a brief speed-up in heart rate, followed by a slow decrease back to the baseline rate. A nice feature of HRT is that Ventricular Premature Contractions (VPCs) occur naturally in most adults, so that measuring the characteristics of a given person's HRT offers a noninvasive way to evaluate his or her cardiac function without applying artificial external stimuli. [2]

In 1999, Georg Schmidt et al. published an article “Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction” demonstrating that the absence of HRT following a PVC amongst patients with a recent acute myocardial infarction served as a risk predictor for Sudden Cardiac Death (SCD) and mortality. As a part of their research, they defined two new parameters, turbulence onset and turbulence slope, which are used to assess HRT. This was a major development since new quantitative independent

[1] http://en.wikipedia.org/wiki/Premature_ventricular_contraction Wikipedia Free Encyclopedia
[2] http://en.wikipedia.org/wiki/Heart_rate_turbulence Wikipedia Free Encyclopedia

indicators able to predict patients with increase probability of SCD or mortality may assist on the early treatment of patients with heart disease.

Since 1999, multiple teams of researchers have been studying a potential link of HRT to the development of many forms of heart disease. As discussed further in the Review of Literature section, the absence of heart rhythm behavior associated with HRT has been known to dissipate in persons with particular types of heart disease; HRT is present in the healthy and absent in the sick.

As research continues to show the correlation between the HRT parameters and SCD, HRT is available to the medical community as predictor of patient deterioration. If the medical community wishes to use HRT, it must understand how the characteristics and limitations of HRT apply to their research environment. Much of the HRT research done so far has been studying by collecting data on monitoring sick human subjects using Holter monitors. For many survivors of sudden cardiac arrest, physician chose to implant cardiac devices, such as Implantable Cardioverter Defibrillators (ICDs), in order to monitor and deliver therapy. Devices such as ICDs collect data from the body and provide physicians with the progression of physiological readings over time. Prior to human clinical studies, medical researchers perform validation of safety and efficacy of Stage III medical devices on animals. For this reason, it is essential that the animal's heart model react similarly to a human heart any limitations when comparing these models is known.

The following paper attempts to show whether a canine's heart has the same HRT effect following a PVC as seen in humans.

2. Background

The following section provides knowledge on biological concepts that are crucial to the discussion of HRT. Certain terms introduced here will be used during the discussion section of this research.

2.1. Canine in Medical Research

Canines are commonly used for cardiac medical research for numerous reasons. Historically, canines were used for practicality reasons; they were easy to obtain then handle and maintain chronically. They have now become the standard for cardiovascular model for researchers.

Canines are also a good model for physiological reasons. The heart of a canine is about 7.5% of its body weight and for humans the proportion is about 4%. Therefore, a big canine's heart approximates a human size heart. There are great similarities in the venous systems, plus access to the venous system is easier due to their low fat content.

Unlike many other animals, canines recover readily from surgery and tolerate anesthesia well. They respond to most CV drugs in a manner similar to humans, except they tend to require higher doses of Beta Blockers for the desired therapeutic effect.

2.2. Sympathetic versus Parasympathetic

The Autonomic Nervous System (ANS) is responsible for the many of the involuntary aspects of our body such as breathing. It regulates the body through stimulation of the body's organs. There are two main competing divisions of the ANS; the sympathetic and parasympathetic nervous systems. The ANS shifts control dependant on the body, therefore their response is usually opposing. In general, the sympathetic nervous system controls the

body's response during times of stress whereas the parasympathetic nervous system controls the body's response during times where energy conservation is preferred. For example, eyes constrict pupils during a parasympathetic response but dilate when the sympathetic nervous system controls.

In respect to the ANS's control of the heart, sympathetic stimulation increases the overall activity of the heart. This is accomplished by increasing both the rate and the force of the heart's contraction. Parasympathetic stimulation causes mainly the opposite effects. To express these in another way, sympathetic stimulation increases the effectiveness of the heart as a pump, as is required during heavy exercise, whereas parasympathetic stimulation decreases its pumping capability but allows the heart some degree of rest between bouts of strenuous activity. [3]

2.3. Cardiac Electrical Signal

Electrocardiograms are a common way of depicting the electrical behavior of the heart. An electrocardiogram is produced by placing electrodes on opposite sides of the heart in order to capture the electrical potentials of current moving through the heart. The electrical characteristics consist of the polarization and depolarization of each chamber of the heart. These electrical phases work in parallel with the mechanical motions of the cardiac cycle; the muscular contractions chambers, which are often used to describe cardiac behavior. Figure 1 shows the correlation between the electrical signal and the ventricular mechanical aspects of a heart beat.

[3] Description taken from the textbook of Medical Physiology page703

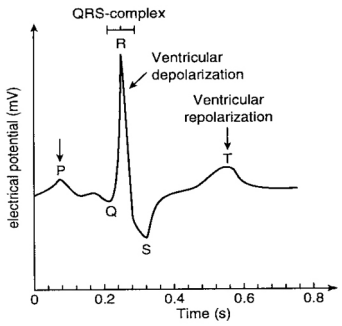

Figure 1 Annotated example of a segment of a normal electrocardiogram [4]

A regular electrocardiogram consists of the combination of both the atrial and ventricular electrical activity. As depicted in the figure above, the P-Wave is the atrial event and the Q-R-S complex reflects the occurrence of the ventricular event, also known as the R-Wave.

The theory behind ideal placement of these leads in order to produce electrocardiograms is Einthoven's Triangle, depicted in Figure 2. Electrodes were conventionally placed on the left leg and both the left and right arms in order to create the 3 signals; Lead I, Lead II and Lead III.

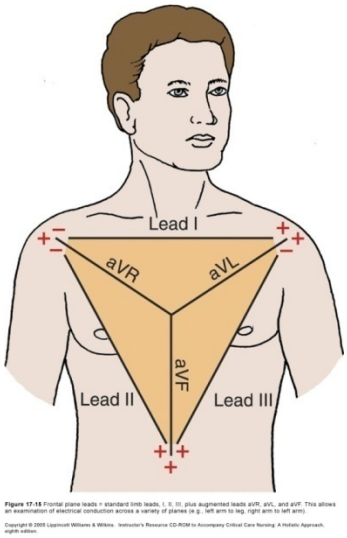

Figure 2 Einthoven's Triangle [5]

[4] Picture from answer.com Health
http://content.answers.com/main/content/img/oxford/Oxford_Sports/0199210896.electrocardiogram.1.jpg
[5] Picture from Connections of Lippincott Williams & Wilkins:
http://connections.lww.com/Products/morton/Ch17.asp

2.4. Heart Rate Turbulence terminology

The following diagram displays some of the terminology discussed related to electrocardiograms (ECGs) and HRT.

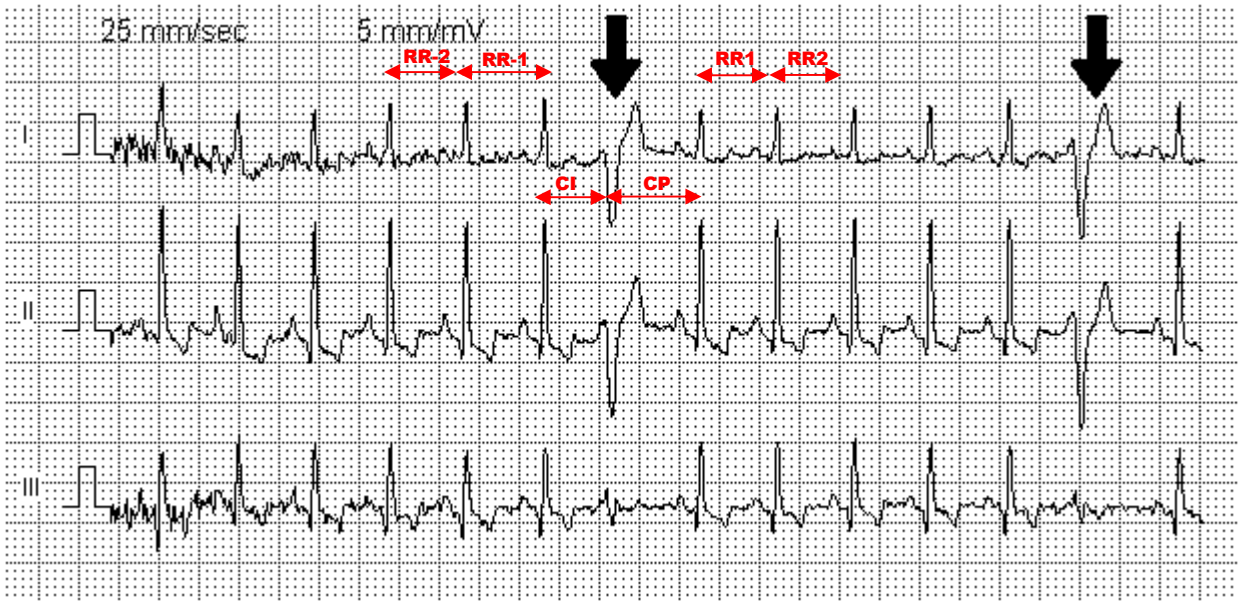

Figure 3 Electrocardiogram with annotation of HRT specific terminology [6]

In Figure 3, the large black arrows point to examples of PVCs. The two normal intervals leading up to the PVC are RR-2 and RR-1. The short interval immediately preceding the PVC is called the Coupling Interval (CI) and the longer interval following is the Compensatory Pause (CP). The events following the CP are sequentially numbered RR1, and RR2. This naming convention will be used throughout the document. As a side note, this electrocardiogram would not be used for studying HRT since there are two PVCs within 15 beats of one another. This will be discussed in more detail further into the document.

[6] Photo (without annotation) from definition of PVC in answers.com http://www.answers.com/topic/premature-ventricular-contraction-1

3. Review of the Literature

In 1999, Georg Schmidt and his team published an article “Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial” which documented their discovery of a new risk factor when discussing the progression of heart disease. These factors were a part of a phenomenon called HRT.

The following section discusses the concept and factors involved in HRT, as documented by Schmidt et al, then a synopsis of how some other researchers have continued the study of the impact of this condition.

By understanding the quantifiers as well as the potential indications of this theory, the significance of characterizing the same behavior in the canine model becomes more pertinent, which will allow for the expansion the possible research and then applications.

3.1. Heart Rate Turbulence

HRT is a simple cardiac behavior. Following a PVC, a healthy heart under normal conditions, increases its heart rate from its base rate to compensate for the extended interval of the PVC, the CP. This behavior is a parasympathetic response; therefore it can be altered through the use of certain drugs.

Through their research documented in “Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial”, Schmidt et al. determined a correlation between the absence of HRT after PVCs and increased risk of mortality post myocardial infarction.

3.2. Heart Rate Turbulence Quantifiers

There are two variables which quantify HRT. Both Turbulence Onset (TO) and Turbulence Slope (TS) can be used independently of one another to determine whether HRT is present. Schmidt et al. also determined that individually both TO and TS served as powerful risk stratifiers through comparison to other factors such as Left-Ventricular Ejection Fraction (LVEF) and high mean base rate.

3.2.1. Turbulence Onset

TO is defined as the percentage difference between the heart rate immediately following PVC and the heart rate immediately preceding PVC.[7] It is calculated using the following equation:

$$\text{Turbulence Onset (TO)} = \frac{(RR1 + RR2) - (RR\text{-}2 + RR\text{-}1)}{RR\text{-}2 + RR\text{-}1} \times 100$$

Where RR1 = Duration of interval immediately following the Compensatory Pause (ms)
RR2 = Duration of interval immediately following RR1 Pause (ms)
RR-1 = Duration of interval immediately prior to the Coupling Interval (ms)
RR-2= Duration of interval immediately prior to RR-1 (ms)

Consult Figure 3 for a diagram displaying the intervals.

If the value of TO is positive, it reflects a deceleration, whereas a positive value reflects an acceleration in the heart rate following a PVC. Therefore, TO less than zero implies the presences of HRT.

[7] Definition of Turbulence Onset from www.h-r-t.com

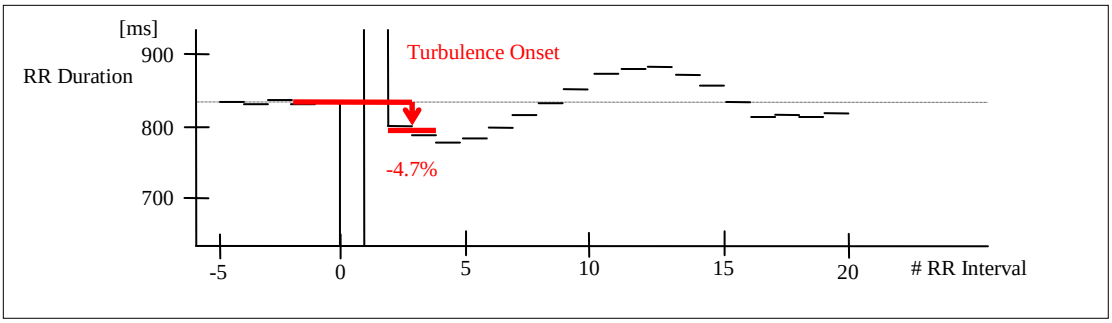

Figure 4 Turbulence Onset Diagram

3.2.2. Turbulence Slope

Schmidt et al. defined Turbulence Slope to correspond to the steepest positive slope of the linear regression line for each sequence of five consecutive sinus intervals found in the 20 sinus-rhythm intervals after the PVC. To determine the slope the equation used was the sum of products divided by the sum of squares.

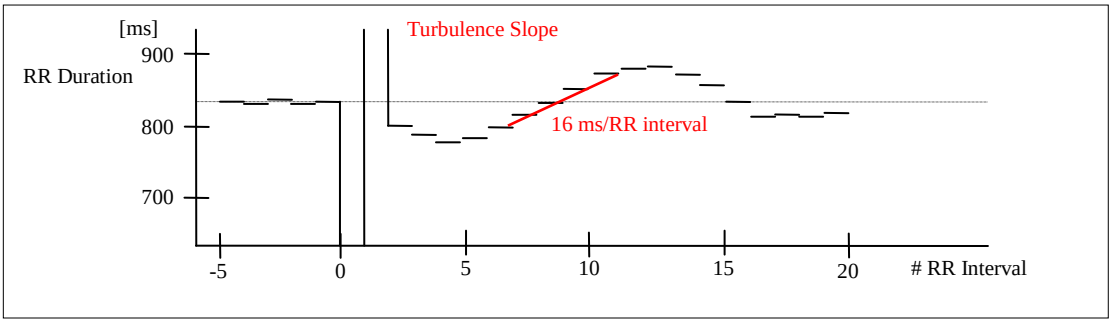

Figure 5 Turbulence Slope Diagram

The units of Turbulence Slope are millisecond per ventricular interval. It is believed that a Turbulence Slope greater than 2.5 ms/interval implies the presence of HRT.

3.3. Original HRT Data Samples

Schmidt et al. had two sample sets that were used to analysis HRT. The first set, the training sample, consisted of 100 patients with coronary artery disease, all of whom had had one or more myocardial infarctions and displayed more than ten PVC per hour during a 24-hour

Holter monitor test. The second set, the validation sample, contained patient data from two studies where patients had survived myocardial infarctions.

The Multicenter Post-Infarction Program (MPIP) study[8] contained 715 survivors of acute myocardial infarction. The European Myocardial Infarction Amiodarone Trial (EMIAT) [9] had a placebo group of 743 patients. Both of these studies used Holter monitors to collect patient's cardiac signal. Patients from these two studies demonstrating atrial fibrillation, a lack of Holter recordings, or a lack of PVCs were excluded from the analysis.

3.4. Subsequent HRT Studies

Following the release of the research done by Schmidt et al. on HRT, many articles were written to test HRT against other cardiac disease states as well as comparing its ability to predict disease state to other more established stratifiers.

"Heart Rate Turbulence and Clinical Prognosis in Hypertrophic Cardiomyopathy and Myocardial Infarction" studied patients in three groups; patients having a history of Myocardial Infarction, those with Hypertrophic Cardiomyopathy and a control set, to determine whether a similar connection between Hypertrophic Cardiomyopathy and HRT could be made. After 27 +/- 10 months of data, the data supported the research from Schmidt et al, but the results did not demonstrate a significant variation in HRT slope and onset for those with Hypertrophic Cardiomyopathy.

The article "Evaluation of Heart-Rate Turbulence as a New Prognostic Marker in Patients With Chronic Heart Failure" examined whether HRT could be used in patients with Chronic

[8] Multicenter Postinfarctions Research Group. Risk stratification and survival after myocardial infarction. N Engl J Med 1983; 309:331-336.
[9] Julian DG, Camm AJ, Frangin G, et al. Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. Lancet 1997; 349: 667-74.

Heart Failure (CHF) to determine the risk of ventricular tachycardia. The study used 24-hr Holter ECG recordings and echocardiography to collect data from 71 patients, 50 of whom had CHF. After 26 +/- 14 months, the study could not conducible correlate HRT with patients with the risk of ventricular tachycardia but it was able correlate a relationship between HRT and CHF patients as well as make links between HRT and other established cardiac risk stratisfiers.

The study further demonstrated that HRT slope was significantly lower in CHF patients versus healthy patients. The article stated "The value of the HRT slope was lower, and the HRT onset was significantly higher than those of the control patients. In particular, the HRT slope (<= 3.0) appeared to be a powerful prognostic marker not only for CHF death but also for CHF hospitalization from worsening CHF. However, the HRT did not appear to reflect the presence of myocardial substrates for VT."

The article also summarized that "It is likely that the HRT slope is more susceptible to CHF events because it correlatives with both the left ventricular function and the cardiac autonomic status; in other words, the HRT slope appears to be a prognostic marker that reflects left ventricular function and cardiac autonomic status." "…both sympathetic and parasympathetic activities may affect the HRT slope."

Another interesting discovery in this research was that in CHF patients, HRT slope was significantly correlated with the LVEF and Standard Deviation for Normal RR Intervals (SDNN) over a 24-hour period. In addition low-frequency/ high-frequency variation of Heart Rate Variation (HRV) and the HRT onset was significantly correlated with SDNN but not with LVEF.

A note on this study is the handling of cardiac drugs by the study population, since drugs could affect HRT values. Though drugs were being used by patients, beta-blockers were transiently stopped before the Holter ECG recordings because they would otherwise affect HRV. Amiodarone was continued.

The article "Association of the Heart Rate Turbulence with Classic Risk Stratification Parameters in Postmyocardial Infarction Patients" studies 509 patients who had had postmyocardial infarction within the past 10 years. After Holter monitor data was collected, both TO and TS were collected for 196 patients. Some of the correlations that came out of the study:

- 58 of patients had a TO displaying HRT, whereas 54 patients had a TS displaying HRT.
- Those with pathological HRT showed decreased HRV values.
- HRT was pathological in 14 out of 24 patients with diabetes mellitus (58%) compared to 40 of 172 (23%) of normoglycemic patients.
- Therapy with beta-blockers had no influence.

The trial also studied 196 patients who had a Myocardial Infarction (MI) prior to 60 years old, and who had a PVC. Age of the MI patients remained significantly associated to decreased TS and TO. HRV was not different. Standard therapy (beta blockers, Angiotensin-Converting Enzyme (ACE) inhibitors, diuretics or calcium channel blockers) had no influence. No association of HRT parameters with the coupling interval or the CP was found. Also the study revealed that "a quarter of all patients with pathological HRT parameters had no conventional pathological risk factor for ventricular arrhythmias such as reduced HRV,

prolonged Corrected QT-Interval (QTc)[10] interval, reduced left ventricular ejection fraction, or left ventricular hypertrophy."

"Assessment of Heart Rate Turbulence in the Acute Phase of Myocardial Infarction for Long-Term Prognosis." also used 24-hour Holter monitors to record PVCs in patients with acute MI. The study compared the HRT quantifiers to other risk factors and concluded of the evaluators, including, HRT (onset and slope), SDNN, mean RR interval, ventricular premature beat frequency, and LVEF, SDNN was the most powerful predicator of mortality among all presumed risk factors in univariate Cox Regression analysis, but in multivariate analysis LVEF and TS were the only independent predictors of mortality.

The journal article "A Phenomenon of Heart-Rate Turbulence, Its Evaluation, and Prognostic Value." restated that the absence of HRT is associated with increased risk of subsequent mortality in cardiac patients. It states that "it is thought that HRT is mediated by baroreflex and therefore can be sued as a non-invasive measure of its sensitivity and autonomic nervous system function." It points out that determining the presence of HRT is easy, non-evasive and cost-efficient so it is a value indicator for the cardiac community.

Though important research was ongoing to assess the usefulness of these new risk factors, there were a few commonalities of the fore-mentioned studies. In each case, the data collected was from human subjects through Holter monitors. Studies involving other means to collect data and other subjects, such as canines or sheep, were not closely analyzed.

[10] QT-interval is the time required to complete depolarization and repolarization. A QT interval above 440 ms is considered prolonged. The Corrected QT-interval is the QT-interval adjusted for heart rate.

4. Materials and Methods

4.1. Study Criteria

There were a few requirements in collecting canine HRT data. The study requirements divided into two categories; subject and data requirements. Attempts to deviate from these requirements were analyzed prior to data collection, and if deemed acceptable, were justified in the test results. The following requirements were used to guide the construction of the HRT research.

4.1.1. Subject-Related Requirements

The subjects must be healthy and non-medicated canines. Disease may cause an absence of HRT response and therefore mislead the research. As discussed previously, a lack of HRT can be an indication of Sudden Cardiac Death (SCD) and mortality therefore the presence of illness can adversely mislead the data of the study. Additionally, HRT is a parasympathetic response and certain medications particularly sedatives, can deviate the body's natural response and skew the collected data.

Both illness and medications in the subject can alter the study data and increase the probability of false-positive data in showing the absence of HRT. If during the data analysis HRT is absent in a subset of subjects, justification would need to be analyzed case-by-case.

As well, a chronic study on multiple subjects is preferred. Since certain aspects of the medical history of the subjects may be unknown, it was important to analysis PVC response in multiple subjects to allow for more confidence statements of the existence or

lack of HRT in canines. Having multiple opportunities to collect data on the same subject provides more reliable data by being able to identify anomalies and providing the capability to average data to better identify general patterns.

4.1.2. Data-related requirements

From the data requirement perspective, the study must provide the means to collect and store at least one ventricular cardiac signal. The ability to detect and quantify the time between intrinsic ventricular cardiac events, including R-waves and PVCs, is required. If the atrial signal is detected, it must be possible to distinguish it from the ventricular signal.

The study must also be able to capture PVCs. Ideally, naturally occurring PVCs that are more than 20 ventricular intervals apart would be ideal, but otherwise, a means to induce PVCs is necessary.

4.2. Study Design and Population

4.2.1. Parent Study

In order to justify the set-up and subject impact required to collect the study data, it was ideal to find an existing study for which to append. Such a study would have to meet the study criteria needed for the HRT research. Fortunately, the opportunity became available. The HRT research data for this experiment was collected as an amendment to an ongoing St Jude Medical canine study conducted by staff scientist Yelena Nabutovsky. This study was ideal for collecting HRT data since it met all the requirements for the study. It was a chronic study of multiple, medication-free subjects. The study had the

ability to collect and store 5 signals including the Right Ventricular signal and could deliver a ventricular pace pulse as a means to induce a PVC.

It is important to note that the parent study protocol defined a need to medicate the canines to allow for additional testing, but HRT data was collected prior to sedation. In a few cases, HRT data was collected while the subject was medicated, but the data collected in those cases were marked as a deviation and analysis was not required for the completion of this study.[11]

The parent study was not modified to collect the HRT data. Amendments were not required to the equipment, number or frequency of data collection sessions and pre and post animal handling. The only modification to the original study was one additional study protocol that was conducted in conjunction with the original study protocol during each collection session. This additional protocol, as submitted to and approved by the lab, is provided as Attachment A and will be discussed in more detail later.

4.2.2. Sample size

The parent study protocol required 6 adult canines supplied by a USDA approved class "A" vendor. Though there were no gender preferences, the study required subjects to be a minimum of 8 months in age and weight of at least 20 kilograms each. In order to assure enough data to be collected, the study protocol stated, "If attrition due to infection should occur, the canine will be replaced, allowing for a maximum of 8 canines for the study."

[11] Though not required, a basic analysis was made of this data and is provided in the discussion section.

The study consisted of a total of 5 canines, who will be referenced by the following arbitrary identifiers; *Canine One*, *Canine Two*, *Canine Three*, *Canine Four* and *Canine Five*.

4.3. Physical Setup

4.3.1. Subject-related equipment

The equipment used in the study included five leads; three subcutaneous SVC coil leads and two intravenous pacing leads. The five leads were implanted and then connected to a standard St Jude Medical Inc 5-port Epic HF[12] header. The location of the three subcutaneous electrodes was placed to mimic Einthoven's Triangle. In order to access the signals from the header, the header was attached to a transcutaneous connector (skin button). The components of the header and skin button can be seen in Figure 6.

Figure 6 St Jude Medical Epic HF Header assembly with trancutaneous connector

[12] St Jude Medical Epic HF Defibrillator Model V-338.is an Implantable Cardioverter Defibrillator (ICD) that also deliver Cardiac Resynchronization Therapy (CRT). It was approved by the FDA on June 30, 2004.

4.3.2. External equipment

Figure 7 shows the equipment setup required for data collection. On the external side, the skin button was connected to the SeaMed 3100 Pacing System Analyzer (PSA) custom-designed stimulator for pacing through the ventricular leads, to amplification hardware and a data acquisition system for collecting data from subcutaneous electrodes.

4.3.3. *Data Analysis Equipment*

No project specific hardware was required for the HRT analysis. Simply a standard personal computer was used to store and analyze the data. There were three main off-the-shelf software applications utilized to analysis the data.

- Matlab 7.0.4.365 (R14) Service Pack 2. Matlab was used to convert the data into a format in which it could be run through project specific tools for analysis. It was also used to graphically display and store the peaks of each file, as well as to graph the resulting averaged signal for a given session.
- Microsoft Excel. Excel was used to store the combined summary of each session. The summary, which is described later, consists of the trims, session specific settings as well as the results for each session. It was also used to easily compare data and maintain a status of the progression of the analysis.
- Microsoft Word. Word was used to document the project.

The original data files were stored on a St Jude Medical CRMD secure server to provide a means to archive and share the data with other researchers.

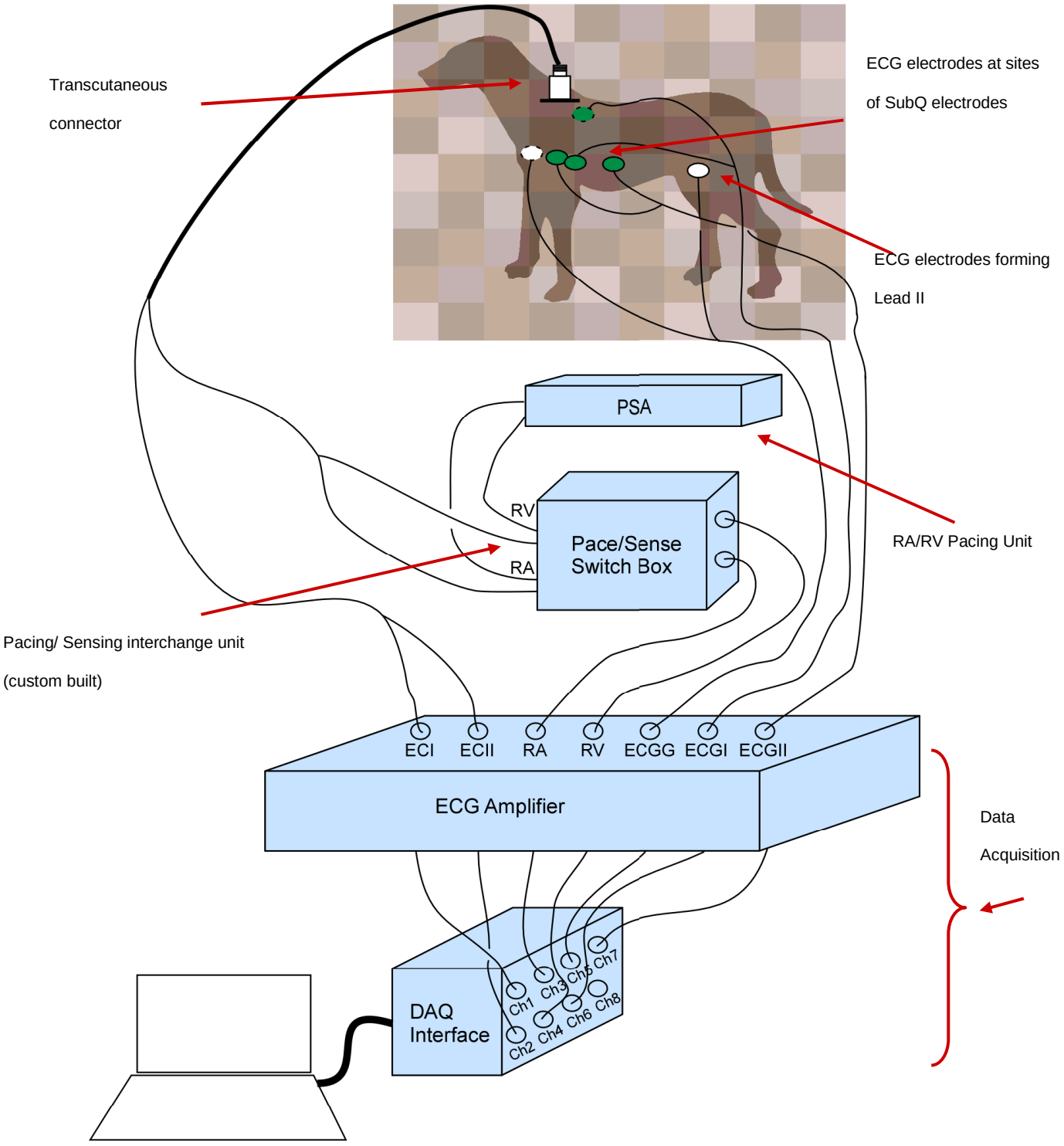

Figure 7 Equipment layout for study

4.4. Data Collection

4.4.1. Electrical Data

As per the parent study, electrical signal data was collected from the subcutaneous electrodes. The electrical signal was passed from the electrodes, through the skin button, and through amplifying electronics to the data acquisition computer.

4.4.2. Data Acquisition

Each canine was scheduled for multiple data collection sessions during the duration of the study. Within this document, a data collection session shall be defined as a consecutive block time spent with an individual canine while a series of tests were performed; following the both the parent study's study plan and the HRT Data Collection Study Plan. The data collection sessions occurred between five days and a month apart. At a data collection session, the HRT Data Collection Study Plan was conducted and the signal data files were stored.

4.4.3. *Protocol*

During a data collection session the canine was made to relax and the steps of the HRT study plan were performed. During each data collection session, thirty records were collected sequentially with a brief pause between each record. The duration of the pause was not deemed significant therefore it was not recorded. Each record contained a PVC.

Applicable segments of the parent study's study plan are provided at Appendix B – Parent Study Plan. Appendix A – Study Plan provides the HRT Data Collection Study Plan as approved by the lab.

If the HRT Data Collection Study Plan were to be used again to collect similar data, an enhancement to the protocol would be recommended. Stating that five consecutive R-Waves are required prior to a successful PVC. If a pace were to occur without successfully causing a PVC, wait 5 R-Waves before trying again. This recommendation will be discussed further in the Discussions section.

Though not mentioned specifically in the study plans, HRT data was collected during the final phase of the Parent Study Plan where the subject was medicated. All HRT data collected on a medicated subject was annotated accordingly. As a result of not being called out in the HRT plan, the medicated HRT data was not collected for all subjects.

4.4.4. *Follow-up*

After implanting the equipment needed for the experiment, the subjects were given time to heal prior to commencing data collection. The pre-data collection delay allowed for the canine to heal and no longer require medication during the data collection phase. The delay prevented the collect of data with a chemically induced alteration of the canine's intrinsic cardiac signal. All HRT data collection sessions were performed at each follow-up for the parent study. As a part of the parent study, it was determined whether the canine was capable to perform the data collection.

4.5. Data Analysis

4.5.1. Overview

The HRT values and statistics were acquired using a data-analyzing tool consisting of a suite of Matlab functions. The process to analyze a given HRT session involves a few

steps. Some steps were automated for repeatability and accuracy and others were manual, due to the need for human inspection (to validate the tool) or based on time-savings, due to the complexity of automation. The scripts used in the automated steps will be defined in further detail in following sections titled Software Tools.

4.5.2. Procedure Inputs

The following statements needed to be true prior to starting the Data Analysis Procedure:

- A directory must exist in which contains all waveform files for a single HRT session. This directory may not contain files from other sessions. Write-access is required for this directory since the Matlab tools created a subdirectory in which the tool outputted additional files. If results of a previous run do not want to be overwritten, then they must be moved or the results directory renamed.
- The file names must be in the format of “pvc” followed immediately by the file number, without a file extension. File numbers should be in sequential order without skipping a number. It is assumed that these files are in chronically order of collection within the session, but this is not required by the tool.
- Note, when defining the trims for a given session, the number of files to be processed is not be the number of files, but the largest number following the name “pvc” in your directory. The tool is smart enough to skip numbers where the file doesn’t exist. Example files names include “pvc1” and “pvc30”.

4.5.3. Trims

Due to the variation of data available for each HRT session, it was necessary to provide a way of tweaking the tool set to perform with increased accuracy for a given data set. For

the context of this HRT study, a trim is a value that can be modified to tailor the tool to better meet the specific needs of the particular HRT data collection session being analyzed. There are nine trims defined in the data analysis tool. The trim values available for a specific HRT session are documented at Appendix D – Raw Data Analysis Results. The following is a description of each trim.

- Trim #1:

  Description: Identifying number of the channel to use. Can be used to find the best signal collected where the PVC and other R-Waves are clear without interference of noise.

  Representation:
  1 = ECI
  2 = ECII
  3 = RA
  4 = RV
  5 = ECGG
  6 = ECGI
  7 = ECGII
- Trim #2:

  Description: Boolean whether to use the inverse of the data stream for detecting the R-Waves. Depending on the setting of Trim #1, this trim will define whether the R or S of the QRS complex is more prominent. If the R is more prominent, this trim should be sent to false, otherwise the tool should detect ventricular events based on the S portion of the complex.

  Representation: true, false

- Trim #3:

  Description: Pre-PVC blanking period. Period immediately prior to the PVC where peak detection is not desired. Since PVCs tend to be large and wide complexes, this trim is used to avoid counting portions of the PVC as other R-Waves.

  Representation: 0 – 2000 ms

- Trim #4:

  Description: Post-PVC blanking period. Period immediately following to the PVC where peak detection is not desired. Since PVCs tend to be large and wide complexes, this trim is used to avoid counting portions of the PVC as other R-Waves.

  Representation: 0 – 2000 ms

- Trim #5:

  Description: Multiplication value for the standard deviation of the peak detection threshold. For over-sensing R-waves, consider increasing the trim value, for under-sensing consider decreasing the value.

  Representation: 0 – 10.0

- Trim #6:

  Description: Boolean whether to use the inverse of the data stream for detecting the PVC complex. PVC complexes tend to have larger amplitude peaks than other sensed events. In some signals, this large peak occurs on the R of the QRS (set trim to false) other times on the S (set trim to true). If PVC detection is not accurate, reconsider this trim value.

  Representation: true, false

- Trim #7:

  Description: Data signal points in each direction that you look for the PVC peak when you use a different orientation of the data for PVC versus peaks. Since the PVC complex is wider than normal intrinsic R-Waves, a large range may be required to find the largest amplitude peak of the complex. This is particularly the case when the values of Trim #2 and Trim #6 are not equivalent.

  Representation: 1 – 1000 ms

- Trim #8:

  Description: Number of points (ms) to ignore at the beginning if the highest peak appears there. This is due to a spike that is sometimes seen at the beginning of the complex.

  Representation: 1 – 1000 ms

- Trim #9:

  Description: Number of files to be processed. This should be the largest number of the data files (pvcX, where X is the largest number). This is not the total number of files.

  Representation: 1 – 50

Note, the trim description provide a representation defining the expected range of the value. Since this tool was only used by the researcher, boundary checking was rarely enforced through the tool and therefore the values given are mere suggestions based on the knowledge of the physiology and the operation of the equipment used for data collection.

Trims are specific to an HRT session and cannot be tailored per data file within the session. This results in files being left out of the analysis due to incorrect annotation by the tool. The concept of annotating data files in discuss in the following section.

4.5.4. Procedure

The following procedure was followed for each data section. With familiarity, the process was improved, as were the tools, but the goal and general functionality remains the same. For several data collection sessions, the data was reanalyzed from a different perspective. In each case, the following procedure was adhered to:

1. Chose the channel to be used.
    - Open any of the data files using the ViewData Matlab tool.
    - Choose which of the five channels has the clearest signal. The ideal signal would have clear R-Wave peaks and the biggest peak would be a clear PVC complex. Input the selected channel into the first trim of the trims defined at the beginning of the ProcessSession Matlab function.
2. Give values to all the trims for the first run. In an editor open up the Matlab file ProcessSession.m. Modify the trims with initial values that seem reasonable based on the current file data.
3. Run the ProcessSession function. The user will be prompted to provide the location of the data files. This shows the tool the current working directory. This tool will generate a window with an annotated EGM for each data file as well as a summary file with the average of all the files in the session.

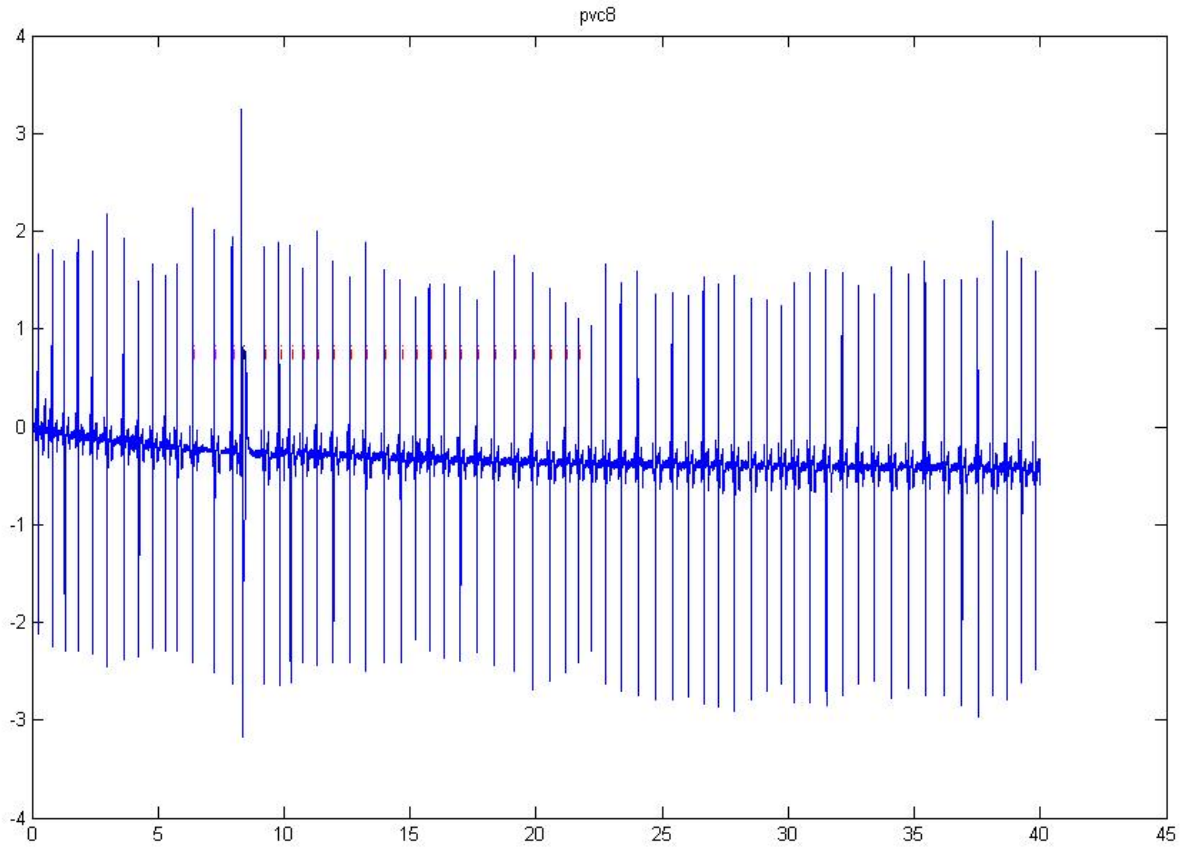

Figure 8 Correctly annotated data sample file (x-axis is time in seconds, y-axis is amplitude)

4. Manually look at each individual annotated EGM and select the final set to be analyzed. For each file, determine whether:
    - The PVC is marked correctly with a black 'I' directly above the X position of the complex. Note if the mark isn't directly above the tip of the PVC complex as expected, consult the value of Trim #7.
    - The pre-PVC peaks are marked correctly with green 'I' markers directly above the X position of the peak of each complex.
    - The post-PVC peaks are marked correctly with red 'I' markers directly above the X position of the peak of each complex.

Sample of a correctly annotated file can be found in Figure 8 (*Canine Four*, 09/27/2004, pvc8), whereas, samples of an incorrectly annotated data sample found can be seen in both Figure 9 and Figure 10. Note, in the correctly annotated file, the PVC and both the pre and post-PVC peaks are marked accordingly. For the incorrect cases, in Figure 9, the data for *Canine Three* 01/04/2005, pvc21 has set the trims to use the inverse of the data to detect the PVC. In this case, the PVC is incorrect marked due to a higher amplitude paced event spike. Under-sensing (pre-PVC) and over-sensing (post-PVC) can also be noted. Figure 10 shows how all trim settings may not be appropriate for every data sample file. In this case, *Canine Three*, 02/15/2005, pvc9, an R-wave is being counted twice at PVC plus 11 due to the value of the standard deviation multiplier for the threshold being set too low.

Keep track of the ones that are not annotated correctly. Modify the trims in order to pass the most number of data files. Note, that the final run should use a trim set that maximizes the number of data files that can be used.

It is possible to have clinically insignificant data files. For example, if data files exist that do not have obvious PVC complexes or multiple PVCs, these files should be removed from the directory and therefore the analysis.

Create a subfolder to store files that will not be used because they aren't clinically significant or they do not pass the algorithm. It is also recommended to remove the generated files found in the results directory immediately prior to the final run, since this will remove outdated figures.

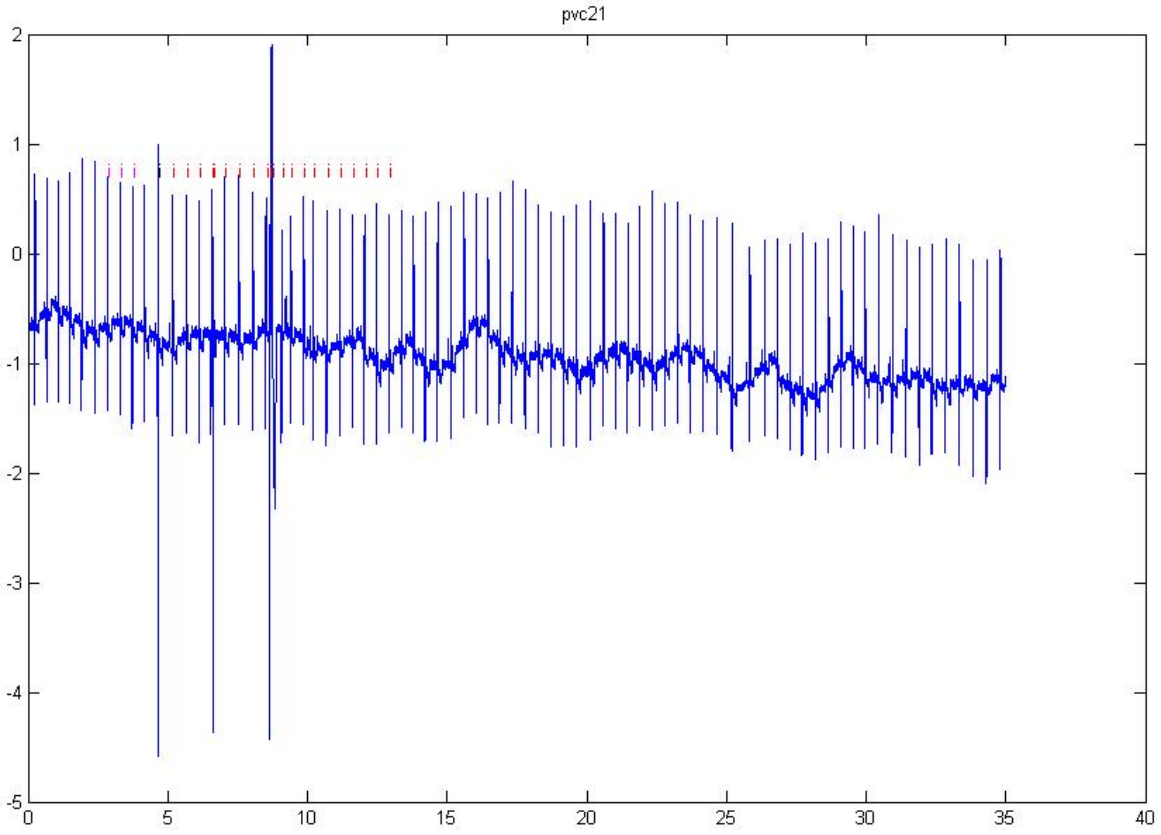

Figure 9 Incorrectly annotated data sample files – Wrong PVC

5. Run the final run for the HRT data session. Manually confirm the output generated to show that the peaks are marked correctly. If an issue is found, return to step 4, otherwise transfer the values stored in the outputted summary file to the Excel spreadsheet. Both of these documents will be discussed in the "Procedure Outputs" section.

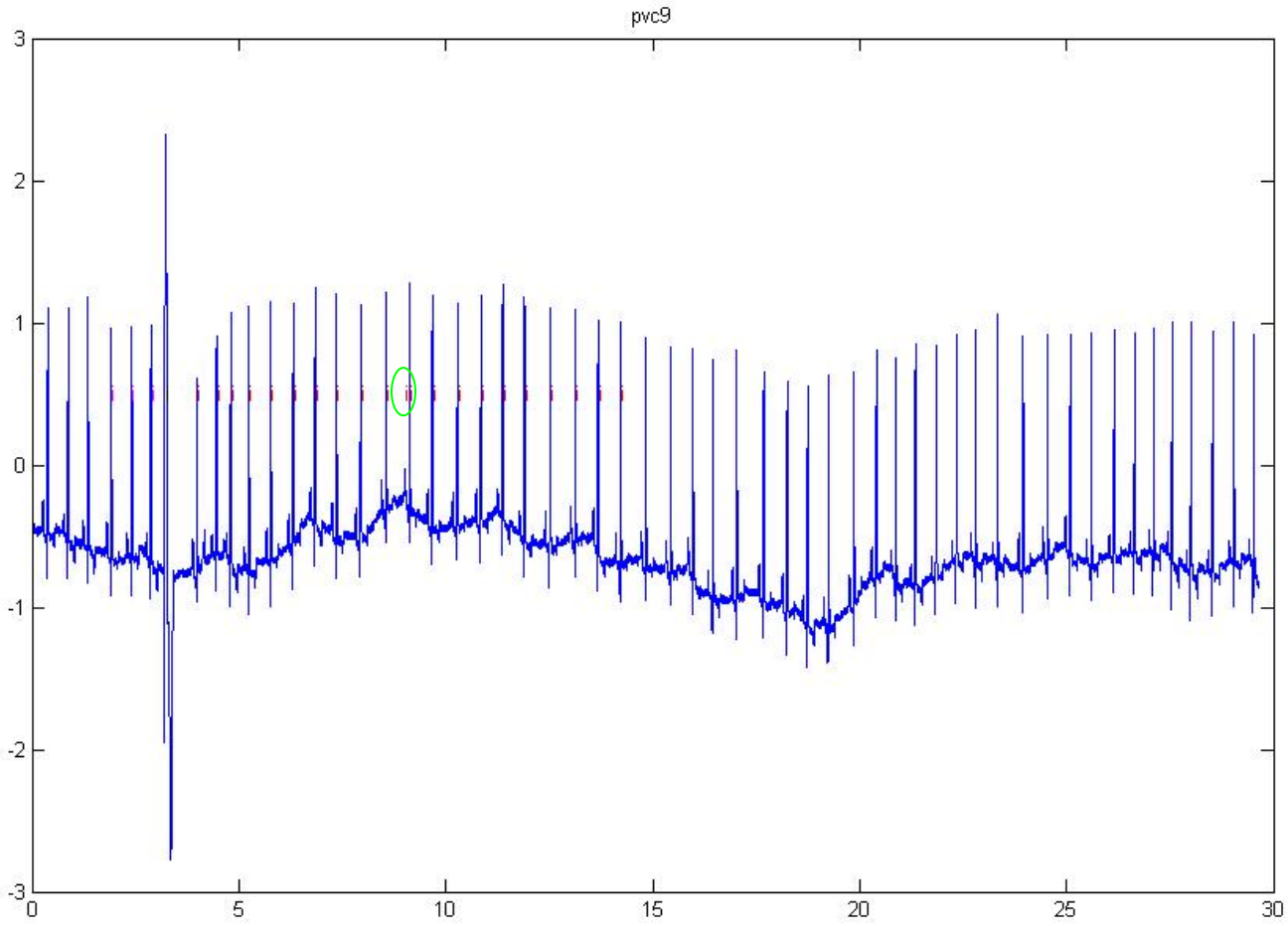

Figure 10 Incorrectly annotated data sample files - Over-sensing

4.5.5. Procedure Outputs

The ProcessSession function does not return any data or information, but it does generate several files. It creates and stores an annotated Matlab figure file for each of the data files within the session. These figures represent each individual stored EGM with the PVC and pre and post R-Waves annotated[13].

A spreadsheet was maintained with at least one row for each data collection session. The columns contained data involving session identification, set-up, extracted data, derived data and notes. Two columns held the data collection session identification, a

[13] These files were created for all data collection sessions. The program automatically saved these files starting only save midway through the data analysis.

combination of canine unique identifier and data. The next column reflected the number of data files used to get the data recorded. Seven columns were devoted for reproducing the set-up and contained the seven trim values used. The extracted average data for each data session was recorded by storing the two intervals prior to the coupling interval (variables RRneg1 and RRneg2), the coupling interval (variable ci), the Compensatory Pause (variable cp) and the two intervals following the CP (variables RR1 and RR2). The derived values are then stored; the Turbulence Onset (variable TO), the maximum slope index and value, the minimum slope and value, and finally the mean and median slope value. The final two columns contained a list of the files omitted and then notes, including the reason for each omission. The final results of this table will be seen in the Results section.

4.5.6. Software Tools - General

Matlab software tools were developed for automating the detection of a session's PVC as well as the R-Waves necessary to the HRT algorithm, in the file. The tool then averaged the session and run the HRT algorithm on the averaged data. The average was chosen since it represents the data without being distracted by the outliers within a particular session.

4.5.7. Software Tools - Definition

The data analysis tools for this project were developed in Matlab. There were 2 main tools called data analysis; ViewData and ProcessSession. These tools called upon lower level functions in order to process the data. The following section has been devoted to

document the functions developed for the data analysis of this project. To view the exact implementation, consult Appendix C – Data Analysis Software for the Matlab code.

"viewData" Function

Input: None

Output: None

Assumptions: None

Project specific functions it calls: None

Description: This function reads in a user specified file and then plots all the channel signals together in one window. Though not used in the HRT calculation, this is a great tool for determining quickly which signal should be used for a given session.

"processSession" Function

Input: None

Output: None

Assumptions: That the data files are numbered pvc1, pvc2, to pvcN and are stored in the same directory.

Project specific functions it calls: readData(), SUMofPRD(), and SUMofSQ()

Description: This is the main application for running a session. It also defines the algorithm trims therefore this file may be modified on each iteration. Note, ideally the trims would be stored in a trim specific data file. The tool starts by prompting the user through a graphical user interface (GUI) for the number of files to be processed. As long as the number of files is not zero, the program will then ask the user to select the first file to be processed, specifically pvc1, though it will only use the directory from the file selected by the user. The program will go from pvc1 to pvcN, where N is the number

provided by the user. The program then creates a matrix where each row represents the summary of each of the data files. It called the readData function to populate the file specific rows. During the collection of data, if information is not available, the row is populated with zeros. Those rows are later removed. Once the matrix creation is complete, algorithm combines the sessions to then calculate specific statistics are performed and the data is plotted and saved to files. The following variables are stored in a summary data file ‘summary.m’.

- 'avgRRIntervals',
- 'RRneg2' – Interval duration of the interval prior to the 'RRneg1'.
- 'RRneg1' – Interval duration of the interval prior to the Coupling Interval.
- 'ci' – Coupling Interval. Interval duration between the ventricular event prior to the PVC to the PVC.
- 'cp' - Compensatory Pause. Interval duration between the PVC and the next ventricular event.
- 'RR1' – Duration of first interval after the Compensatory Pause.
- 'RR2'– Duration of second interval after the Compensatory Pause.
- 'TO' – Turbulence Onset.
- 'slopeResults' – An array containing the slope of the R-R intervals. Each slope is calculated based on the sum of products divided by the sum of squares of each 5 sequential ventricular intervals.
- 'maxslopevalue' – Highest slope amplitude found in slopeResults.
- 'maxslopeindex' – The index within slopeResults of the highest slope amplitude.
- 'minslopevalue' – Minimum slope amplitude found in slopeResults.

- 'minslopeindex' – The index within slopeResults of the minimum slope amplitude.
- 'medianslopevalue' – Mathematic median of the slope amplitudes.
- 'meanslopevalue' – Mathematic mean of the slope amplitudes.
- 'indices' – Two-dimensional matrix which contains all the valid data for a given session. All of the statistics for this session are driven from this matrix. For indices(row,column), each row represents a valid pvc data file. Valid data reflects that there is a non-zero value in each of the columns of a particular row. Invalid data has been removed. There are 25 columns. Each column represents a ventricular event in chronological order, represented by its index into the original data signal file (pvcN). The data files are matched up where the 4th column represents the PVC.

As an enhancement to the data collected, about half the sessions have the grafts of the intervals of each specific file as well.

"Readdata" Function

Input: path: Directory of the current session.

fid: File Identifier as returned by fopen()

H: Figure number being plotted on.

fileN: Number of the current file being processed.

trims: array of 9 values as defined.

Output: CLs: Cycle Lengths for that channel in milliseconds

indVector: Signal indices of the R-Waves

Assumptions: None

Project specific functions it calls: HRTpeaks()

Description: This function was written by Yelena Nabutovsky and was provided as a means to read the data. It reads the signal data of the channel specified in the trims and sends it to HRTPeaks for analysis.

"HRTPeaks" Function

Input: path: Directory of the current session.

signal: Signal to be analyzed

fs: Sampling frequency.

H: Figure number being plotted on.

fileN: Number of the current file being processed.

trims: array of 9 values as defined.

Output: CLs: Cycle Lengths for that channel in milliseconds

indVector: Signal indices of the R-Waves

Assumptions: None

Project specific functions it calls: GetPeaks()

Description: This takes the signal data and determines the PVC as well as the pre and post peaks. It also plots the data marking the pre-peaks, post-peaks and the PVC in different colors. The plots are used to analyze whether the PVC and other R-Wave were correctly identified by the tool.

"getPeaks" Function

Input: data: signal

Output: ind: array of indices marking the peaks of the signal

Assumptions: None

Project specific functions it calls: None

Description: This program finds indices of peaks in a given signal input is data, which is the data to be analyzed output is ind, which is a vector of peak indices.

"SUMofSQ" Function

Input: X: X-axis values to be calculated as an array.

Output: SSx: The sum of squares.

Assumptions: None

Project specific calls:None

Description: Generic function which determines the sum of squares of the X values in the array.

"SUMofPRD" Function

Input: X: X-axis values to be calculated as an array.

Y: Y-axis values to be calculated as an array.

Output: SPxy: The sum of products.

Assumptions: None

Project specific calls: None

Description: Generic function which determines the sum of products of the X and Y arrays provided.

4.5.8. Statistics

The HRT data analysis tools were created to analysis each data file and then compile the results in order to average the data, to get the average signal for the data collection session. Once the averaged RR intervals were determined, the following statistics were collected.

- TS
- TO
- Maximum Slope Index and Value following the PVC
- Mean Slope Value following the PVC
- Median Slope Value following the PVC

All slopes are based on 5 consecutive intervals following the PVC.

Note that these values are unique to the data collection session, the subset of data files used, and the trim values used, therefore it is possible to get different results for a given data collection session.

5. Results

The data presented below was extracted from the master spreadsheet found at Appendix D – Raw Data Analysis Results. Note that 27 of the 28 data collection sections are featured below. One session was never processed due to the lack of quality of the signal in all channels. It will be discussed further in the Discussion section below. All runs that had to have the analysis redone to improve the accuracy were eliminated from the data presented below.

5.1. Trims used

In order for all the data collection sessions to be able to use the same tools, the tool used trims, customizable values used to tweak the tool to better process a given data collection section. The table below expresses the trims used for all valid runs of the data analysis tool.

Subject	Date	Numbers of files used	Channel Number Used Trims(1)	Negative Data Stream? Trims(2)	Pre-PVC blanking period Trims(3)	Post-PVC blanking period Trims(4)	Multiplication value for Std Dev of Threshold Trims(5)	Use of Inverse Data for the PVC? Trims(6)	Look for a PVC in each direction, when data & PVC is of opposite polarity Trim(7)	Duration to ignore peaks at the beginning of file Trim(8)	Number of files Trim(9)
Canine One	9/1/2004	11	7	TRUE	0	320	2.19	FALSE	120	35	30
Canine Two	1/25/2005	19	5	TRUE	50	320	3.50	TRUE	70	35	30
Canine Two	10/21/2004	9	2	FALSE	25	320	2.19	TRUE	70	35	30
		12	2	FALSE	0	350	2.19	TRUE	120	35	30
		9	2	FALSE	0	350	2.19	TRUE	120	35	30
Canine Two	10/26/2004	20	5	TRUE	30	320	2.40	FALSE	70	35	30
		13	5	TRUE	30	320	2.40	FALSE	70	35	30
Canine Two	11/1/2004	13	2	FALSE	28	320	2.10	TRUE	70	35	30
		15	2	FALSE	26	320	2.40	TRUE	70	35	30
Canine Two	12/21/2004	25	5	TRUE	70	320	2.00	FALSE	150	35	30
Canine Two	1/26/2005	18	1	TRUE	290	330	2.40	FALSE	70	35	30
Canine Three	1/4/2005	18	2	FALSE	30	320	2.40	TRUE	70	35	30
Canine Three	1/25/2005	30	2	FALSE	10	320	1.90	FALSE	70	35	30
		18	2	FALSE	10	320	1.90	FALSE	70	35	30
Canine Three	2/8/2005	21	2	FALSE	35	320	2.50	FALSE	70	35	30
Canine Three	2/15/2005	25	2	FALSE	31	250	3.40	FALSE	70	25	30
Canine Three	3/8/2005	15	2	TRUE	1	500	3.40	FALSE	70	35	30
Canine Four	9/21/2004	9	2	TRUE	15	320	1.90	FALSE	70	25	30
Canine Four	9/27/2004	21	7	TRUE	1	320	2.20	FALSE	70	35	31
		16	7	TRUE	1	320	2.20	FALSE	70	35	31

Subject	Date	Numbers of files used	Channel Number Used Trims(1)	Negative Data Stream? Trims(2)	Pre-PVC blanking period Trims(3)	Post-PVC blanking period Trims(4)	Multiplication value for Std Dev of Threshold Trims(5)	Use of Inverse Data for the PVC? Trims(6)	Look for a PVC in each direction, when data & PVC is of opposite polarity Trim(7)	Duration to ignore peaks at the beginning of file Trim(8)	Number of files Trim(9)
Canine Four	10/7/2004	24	6	TRUE	1	320	1.80	FALSE	70	35	30
Canine Four	10/13/2004	17	2	TRUE	1	320	2.20	FALSE	70	35	30
Canine Four	10/21/2004	24	5	TRUE	25	320	2.19	FALSE	70	35	30
Canine Four	10/26/2004	29	2	TRUE	1	320	1.90	FALSE	70	35	30
Canine Four	11/1/2004	23	5	TRUE	25	320	1.80	FALSE	70	35	30
		18	5	TRUE	25	320	1.80	FALSE	70	35	30
Canine Four	12/21/2004	27	2	TRUE	1	320	1.80	FALSE	70	35	30
Canine Four	1/4/2005	9	1	TRUE	50	300	2.90	TRUE	70	35	15
Canine Five	1/4/2005	16	2	FALSE	1	320	2.20	FALSE	70	35	30
Canine Five	1/25/2005	21	2	FALSE	1	320	2.20	FALSE	70	35	30
		18	2	FALSE	1	320	2.20	FALSE	70	35	30
Canine Five	2/15/2005	15	2	FALSE	1	320	1.80	FALSE	70	35	30
Canine Five	3/8/2005	27	2	FALSE	10	250	2.50	TRUE	150	25	30
Canine Five	3/29/2005	17	2	FALSE	10	300	3.90	TRUE	200	35	30
Canine Five	3/29/2005	22	2	TRUE	10	300	2.90	TRUE	70	35	30

Table 1 Trims used for valid analysis of HRT data

On average, 18 out of 30 files, 60%, were used to create the averaged data sample. ECII (63%) and ECGG (19%) were the two most commonly used signal channels. Interestingly, all signals were used except the 2 leads channels. Both RA and RV signals were never selected to process the data.

5.2. HRT data collection session data

As discussed earlier, with only one exception, at least 30 data samples were collected for each data collection session. In order to average out the outliers, once a subset trims were selected to use the largest subset of the 30 data samples through the tool, the tool would create a matrix of intervals of the ventricular events. Each row represented one data sample. To align the data, only the intervals of interest to the HRT algorithm were stored for each data sample. The first column contains the second interval prior to the Coupling Interval

(RRneg2), and then it was each ventricular interval subsequent until 20 intervals follow the CP. The tool would then find the average of each column and then store it into a next 1-by-24 matrix containing the averaged results of this data. This data was also plotted for each data collection session.

The following was the sample graph of the average HRT data:

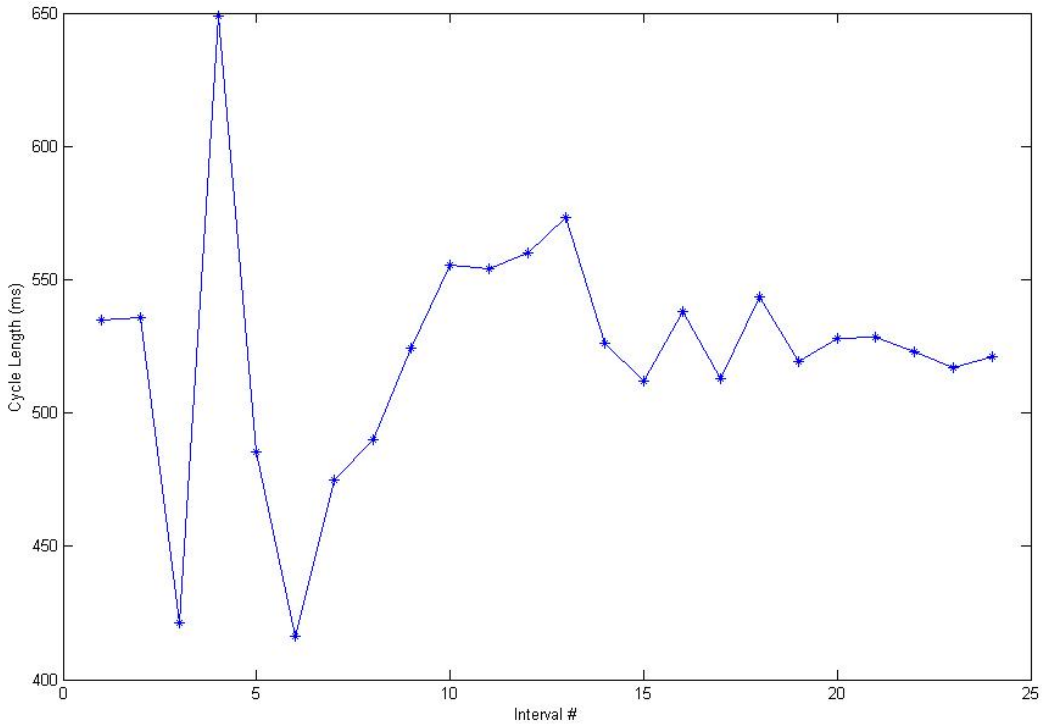

Figure 11 Plot of averaged data for *Canine Five* dated 01/04/2005

5.3. HRT data summary

The following table contains all the data analysis runs performed sorted by data collection session.

Subject	Date	RR-2 (ms)	RR-1 (ms)	Coupling Interval (ms)	Compensatory Pause after VPB (ms)	RR1 (ms)	RR2 (ms)	Turbu-lence Onset	Max Slope Index	Max Slope (ms/ interval)	Min Slope Index	Min Slope (ms/ interval)	Median Slope (ms/ interval)	Mean Slope (ms/ interval)
Canine One	9/1/2004	732.0909	701.1818	494.1818	723.0000	663.8182	622.4545	-0.1026	8	9.7727	15	-15.8182	-0.5273	-1.2273
Canine Two	1/25/2005	696.8947	638.2105	531.4211	803.7368	595.4211	591.4737	-0.1110	2	29.1632	5	-21.9737	-0.3000	1.7400
Canine Two	10/21/2004	504.4444	525.1111	545.0000	854.4444	629.1111	478.7778	0.0761	9	37.4889	12	-41.9778	6.6889	2.4874
		497.1667	574.1667	568.6667	791.0000	539.7500	476.0000	-0.0519	2	42.2500	6	-26.5333	6.4083	4.6128
		519.4444	582.5556	585.6667	778.8889	580.8889	484.8889	-0.0329	2	47.7778	6	-32.3556	5.9778	4.5333
Canine Two	10/26/2004	677.5500	697.3000	490.3000	873.0000	566.6000	706.4000	-0.0741	1	61.9950	5	-42.6400	-2.7600	2.9283
		691.2308	717.4615	495.6154	850.0000	583.8462	661.5385	-0.1159	1	55.7462	5	-43.4154	-1.5000	6.0744
Canine Two	11/1/2004	611.3077	668.9231	467.0769	842.9231	573.0769	532.2308	-0.1366	2	36.7000	5	-17.2538	5.1538	5.9421

Subject	Date	RR-2 (ms)	RR-1 (ms)	Coupling Interval (ms)	Compensatory Pause after VPB (ms)	RR1 (ms)	RR2 (ms)	Turbu-lence Onset	Max Slope Index	Max Slope (ms/ interval)	Min Slope Index	Min Slope (ms/ interval)	Median Slope (ms/ interval)	Mean Slope (ms/ interval)
		633.2000	667.2000	475.8000	842.8667	561.9333	530.3333	-0.1601	1	33.5333	14	-20.1733	5.1467	5.2431
Canine Two	12/21/2004	772.5200	810.7600	594.0800	1060.6000	723.4800	651.0800	-0.1318	2	58.1400	13	28.8600	-0.1400	7.0856
Canine Two	1/26/2005	693.0000	691.0556	790.3889	596.0000	679.2222	638.4444	-0.0480	2	14.2000	14	-0.4500	0.1000	2.1385
Canine Three	1/4/2005	481.8889	498.8889	365.5556	617.1111	439.3889	400.3889	-0.1438	2	25.0444	9	-3.2889	1.0444	3.8926
Canine Three	1/25/2005	546.7333	554.9667	406.0667	632.6667	550.9000	545.9667	-0.0044	3	16.9400	7	-8.2533	-0.3667	0.6171
		552.4444	561.0556	417.0000	647.6111	486.4444	470.0556	-0.1410	2	24.4222	7	-13.9111	2.4944	3.3107
Canine Three	2/8/2005	546.1905	542.9048	407.1429	642.8571	504.3333	473.0952	-0.1025	2	17.1667	9	-8.0330	4.6238	4.4463
Canine Three	2/15/2005	587.4400	575.6000	423.2800	738.0400	538.0800	480.6400	-0.1241	2	33.3120	9	-12.2960	3.9000	6.8171
Canine Three	3/8/2005	999.7333	995.6667	640.2000	1000.6000	875.2000	995.6000	-0.0624	1	26.6467	7	-6.5200	1.2133	1.7920
Canine Four	9/21/2004	530.2222	536.3333	359.2222	627.3333	494.0000	458.5560	-0.1069	2	34.3444	10	-16.7780	6.5111	5.7489
Canine Four	9/27/2004	670.5714	709.4286	502.0000	794.3333	626.2381	604.0000	-0.1085	1	39.9190	4	-23.4524	-2.5190	1.5860
		676.0625	733.0000	516.8125	835.8125	582.2500	552.0625	-0.1950	1	45.2813	4	-16.3687	1.2000	4.4975
Canine Four	10/7/2004	633.7083	626.8750	417.4583	825.3333	565.6667	540.5000	-0.1225	2	27.7208	7	-8.7833	0.8833	4.2675
Canine Four	10/13/2004	673.5294	746.7647	476.3529	906.4118	639.8235	642.5294	-0.0971	1	36.1000	3	-23.5941	0.1529	0.4706
Canine Four	10/21/2004	701.1304	769.4783	578.1739	766.6957	635.0870	698.3478	-0.0933	1	45.0435	7	-17.4174	-4.1913	1.2841
Canine Four	10/26/2004	530.2200	536.3300	359.2200	627.3300	494.0000	458.5600	-0.1069	2	34.3444	10	-16.7778	6.5111	5.7489
Canine Four	11/1/2004	635.0870	752.2609	568.2174	878.8261	692.7826	634.8261	-0.0431	2	49.8391	6	-30.4739	1.2174	2.8061
		635.7222	755.0000	542.3333	880.0000	624.0556	589.1667	-0.1276	2	76.4944	5	-48.8278	4.5667	6.3467
Canine Four	12/21/2004	653.7778	673.7407	412.6667	776.7037	597.3333	565.2222	-0.1243	1	40.9185	5	-12.8778	-2.0778	3.5415
Canine Four	1/4/2005	521.2222	521.7778	403.7778	653.5556	518.5556	446.8889	-0.0744	2	15.4667	8	-0.6889	0.5333	1.8304
Canine Five	1/4/2005	534.9375	535.8125	421.3750	648.6875	485.2500	416.4375	-0.1579	2	32.7375	7	-11.7688	1.6000	4.1413
Canine Five	1/25/2005	669.4762	715.0476	447.0952	796.8095	577.7143	576.0952	-0.1666	1	49.7619	4	-30.2571	0.5905	1.5749
		686.6111	728.2222	435.1667	791.5556	534.0000	559.6667	-0.2270	1	68.7667	4	-37.7111	-0.1833	2.6496
Canine Five	2/15/2005	642.7333	677.9333	633.6667	859.8667	712.2000	620.0000	0.0087	1	57.9200	9	-49.1067	-1.0867	1.3236
Canine Five	3/8/2005	767.6667	746.6667	575.0000	833.9630	781.5185	761.0000	0.0186	3	25.1481	15	-31.2333	0.9444	-1.1842
Canine Five	3/29/2005	661.5714	851.0000	789.6429	922.9286	1083.5000	941.8571	0.3390	3	101.4786	6	-52.5214	-1.1429	-9.6643
Canine Five	3/29/2005	637.4000	635.6500	413.8500	826.5500	558.0000	592.9500	-0.0959	1	18.7600	14	-1.4600	0.3350	2.0083

Table 2 Final summary of averaged data collection sessions

5.4. Classification

The general pattern of the data would be the two intervals prior to the Coupling Interval would be at the canine's base rate, followed by a short Coupling Interval (due to the early occurrence of the PVC), and then followed by a long CP. In the presence of HRT the events following the CP would be fast than base rate, otherwise those intervals would remain at base rate.

The original article on HRT by Schmidt et al. stated that a TO less than zero and a TS greater than or equal to 2.5 ms/RR interval would reflect the existence of HRT. Provided these numbers, the following table was abstracted:

Subject	Date	RR-2 (ms)	RR-1 (ms)	Coupling Interval (ms)	Compensatory Pause after VPB (ms)	RR1 (ms)	RR2 (ms)	Turbu-lence Onset	Max Slope Index	Max Slope (ms/ interval)	Sequence of events as expected for HRT?	HRT Turbu-lence Onset?	HRT Slope?	Is Explant?
Canine One	9/1/2004	732.0909	701.1818	494.1818	723.0000	663.8182	622.4545	-0.1026	8	9.7727	No	Yes	Yes	No
Canine Two	1/25/2005	696.8947	638.2105	531.4211	803.7368	595.4211	591.4737	-0.1110	2	29.1632	Yes	Yes	Yes	No
Canine Two	10/21/2004	504.4444	525.1111	545.0000	854.4444	629.1111	478.7778	0.0761	9	37.4889	No	No	Yes	No
		497.1667	574.1667	568.6667	791.0000	539.7500	476.0000	-0.0519	2	42.2500	No	Yes	Yes	No
		519.4444	582.5556	585.6667	778.8889	580.8889	484.8889	-0.0329	2	47.7778	No	Yes	Yes	No
Canine Two	10/26/2004	677.5500	697.3000	490.3000	873.0000	566.6000	706.4000	-0.0741	1	61.9950	No	Yes	Yes	No
		691.2308	717.4615	495.6154	850.0000	583.8462	661.5385	-0.1159	1	55.7462	Yes	Yes	Yes	No
Canine Two	11/1/2004	611.3077	668.9231	467.0769	842.9231	573.0769	532.2308	-0.1366	2	36.7000	Yes	Yes	Yes	No
		633.2000	667.2000	475.8000	842.8667	561.9333	530.3333	-0.1601	1	33.5333	Yes	Yes	Yes	No
Canine Two	12/21/2004	772.5200	810.7600	594.0800	1060.6000	723.4800	651.0800	-0.1318	2	58.1400	Yes	Yes	Yes	No

Subject	Date	RR-2 (ms)	RR-1 (ms)	Coupling Interval (ms)	Compensatory Pause after VPB (ms)	RR1 (ms)	RR2 (ms)	Turbu-lence Onset	Max Slope Index	Max Slope (ms/ interval)	Sequence of events as expected for HRT?	HRT Turbu-lence Onset?	HRT Slope?	Is Explant?
Canine Two	1/26/2005	693.0000	691.0556	790.3889	596.0000	679.2222	638.4444	-0.0480	2	14.2000	Yes	Yes	Yes	Yes
Canine Three	1/4/2005	481.8889	498.8889	365.5556	617.1111	439.3889	400.3889	-0.1438	2	25.0444	Yes	Yes	Yes	No
Canine Three	1/25/2005	546.7333	554.9667	406.0667	632.6667	550.9000	545.9667	-0.0044	3	16.9400	No	Yes	Yes	No
		552.4444	561.0556	417.0000	647.6111	486.4444	470.0556	-0.1410	2	24.4222	Yes	Yes	Yes	No
Canine Three	2/8/2005	546.1905	542.9048	407.1429	642.8571	504.3333	473.0952	-0.1025	2	17.1667	Yes	Yes	Yes	No
Canine Three	2/15/2005	587.4400	575.6000	423.2800	738.0400	538.0800	480.6400	-0.1241	2	33.3120	Yes	Yes	Yes	No
Canine Three	3/8/2005	999.7333	995.6667	640.2000	1000.6000	875.2000	995.6000	-0.0624	1	26.6467	Yes	Yes	Yes	Yes
Canine Four	9/21/2004	530.2222	536.3333	359.2222	627.3333	494.0000	458.5560	-0.1069	2	34.3444	Yes	Yes	Yes	No
Canine Four	9/27/2004	670.5714	709.4286	502.0000	794.3333	626.2381	604.0000	-0.1085	1	39.9190	Yes	Yes	Yes	No
		676.0625	733.0000	516.8125	835.8125	582.2500	552.0625	-0.1950	1	45.2813	Yes	Yes	Yes	No
Canine Four	10/7/2004	633.7083	626.8750	417.4583	825.3333	565.6667	540.5000	-0.1225	2	27.7208	Yes	Yes	Yes	No
Canine Four	10/13/2004	673.5294	746.7647	476.3529	906.4118	639.8235	642.5294	-0.0971	1	36.1000	Yes	Yes	Yes	No
Canine Four	10/21/2004	701.1304	769.4783	578.1739	766.6957	635.0870	698.3478	-0.0933	1	45.0435	Yes	Yes	Yes	No
Canine Four	10/26/2004	530.2200	536.3300	359.2200	627.3300	494.0000	458.5600	-0.1069	2	34.3444	Yes	Yes	Yes	No
Canine Four	11/1/2004	635.0870	752.2609	568.2174	878.8261	692.7826	634.8261	-0.0431	2	49.8391	No	Yes	Yes	No
		635.7222	755.0000	542.3333	880.0000	624.0556	589.1667	-0.1276	2	76.4944	Yes	Yes	Yes	No
Canine Four	12/21/2004	653.7778	673.7407	412.6667	776.7037	597.3333	565.2222	-0.1243	1	40.9185	Yes	Yes	Yes	No
Canine Four	1/4/2005	521.2222	521.7778	403.7778	653.5556	518.5556	446.8889	-0.0744	2	15.4667	Yes	Yes	Yes	Yes
Canine Five	1/4/2005	534.9375	535.8125	421.3750	648.6875	485.2500	416.4375	-0.1579	2	32.7375	Yes	Yes	Yes	No
Canine Five	1/25/2005	669.4762	715.0476	447.0952	796.8095	577.7143	576.0952	-0.1666	1	49.7619	Yes	Yes	Yes	No
		686.6111	728.2222	435.1667	791.5556	534.0000	559.6667	-0.2270	1	68.7667	Yes	Yes	Yes	No
Canine Five	2/15/2005	642.7333	677.9333	633.6667	859.8667	712.2000	620.0000	0.0087	1	57.9200	No	No	Yes	No
Canine Five	3/8/2005	767.6667	746.6667	575.0000	833.9630	781.5185	761.0000	0.0186	3	25.1481	No	No	Yes	No
Canine Five	3/29/2005	661.5714	851.0000	789.6429	922.9286	1083.5000	941.8571	0.3390	3	101.4786	No	No	Yes	No
Canine Five	3/29/2005	637.4000	635.6500	413.8500	826.5500	558.0000	592.9500	-0.0959	1	18.7600	Yes	Yes	Yes	Yes

Table 3 Final Analysis Results

Note an additional column was added to the table above in order to address data collected at time of explant. Prior to these data collection sessions, the canine was given sedatives.

In every data collection session the TS was greater than 2.5 ms/RR interval and therefore reflected that HRT was present in these canines. In 23 of 27 data collection sessions had a TO less than zero, implying the presence of HRT. Though it will be addressed in the next section, 3 out of 4 of the remaining sessions were associated to the same canine. The fourth data collection session was reanalyzed from a different perspective and found HRT to be present though the TO and TS values were low.

6. Discussion

The results shown above favor that the canines did display signs of HRT, the data and the results yielded interesting phenomenon which will be discussed in further detail. These discussion topics fall in five main topics. Firstly, the affects of sedation will be considered. This will be followed by a discussion of the study challenges and limitations and their impact. Since the data implied that canines do have HRT, potential application and future research will discuss the importance of these results.

6.1. Sedation

The sedation medication given to the canines prior to explant provided interesting HRT Data. In every case the medication seemed to decrease the TS values and in all but one case decrease the TO values compared to the average for that canine, but HRT was still present based on both the TO and TS for each.

An interesting case is *Canine Five* dated 3/29/2005. Before sedation, *Canine Five*'s TO was greater than zero, but following sedation, the TO decreased to below zero. This would imply that the HRT did not appear until after sedation. It was noted that for the data collection prior to sedation the base rate had large fluctuation which could impacted the TO value. The large drop in TS after sedation would support this.

6.2. Study challenges

There were different types of challenges on this project. Some were known and had to be addressed prior to conducting the data collection. Whereas, others were identified during the

studied and those need their impact to be analyzed. These types of challenges may lead to future research projects.

The largest challenge in performing this study was finding the most true research environment for observing PVC in canines. Firstly, HRT is a parasympathetic response to a premature beat. Many medications inhibit such a response. Finding a research project that did not sedate the animals, yet made the other criteria became a challenge. This challenge was solved in order to conduct the research.

Another challenge arose on how to assess canines that didn't display HRT. In three data collection sessions, all with the same canine, the TO value calculated for the canine indicated a lack of HRT. Since research has shown that a human can fail to display HRT when suffering from certain types of heart disease, the true reason for the lack of HRT in these 3 sessions is not known. The same canine did have sessions where the TO was less than zero, indicating HRT. Without a complete medical history of the canine and many other diagnostic tests run on the canine, medical complications may have played a factor in the results.

Several concerns arose based on observing the data which was collected. Firstly, consideration was made to whether other physiological condition could affect the HRT quantifiers. The most obvious of these concerns was the fluctuation of the canine's base heart rate. Many physiological factors including breathing can have cause Heart Rate Variability (HRV). In some canines, large fluctuations were found in canines which caused the heart rate to speed up and slow down. HRV, if severe, could affect the values of the HRT quantifiers. By averaging the data files for a given data collection elevated this concern for most sessions, but with really high HRV during a session, the data could still be skewed.

High fluctuations in heart rate can cause unexpected data points. For example, based on the HRT algorithm, one would assume that the maximum slope in the 20 events following the PVC should occur starting soon after the PVC as the compensation occurs for the CP. In two data collection sessions the maximum slope occur at least five ventricular events after the PVC (maximum slope index was greater than five). One of these cases, the canine's TO did not detect HRT. In two cases, the final analysis of the canine's rhythm had a maximum slope at starting at index 3. Both of these cases were *Canine Five*, which was the other canine to have a TO which did not detect HRT. Though the HRT algorithm states that any slope within 20 ventricular events following the PVC, the compensation, and thus increased heart rate, is expected within a few events.

Another concern was whether the method of artificially creating PVCs by pacing into an intrinsic ventricular sensed event cause side-effects. Concerns exists that the artificial provocation of PVCs introduced other anomalies. Occasionally in the research data, more frequent with particular data collection sessions, the PVC would capture followed by a shorter CP, followed by a long interval RR1 and then multiple fast beats. A sample of this can seen in the below figure based on data file 8 from *Canine Five* dated 02/15/2005.

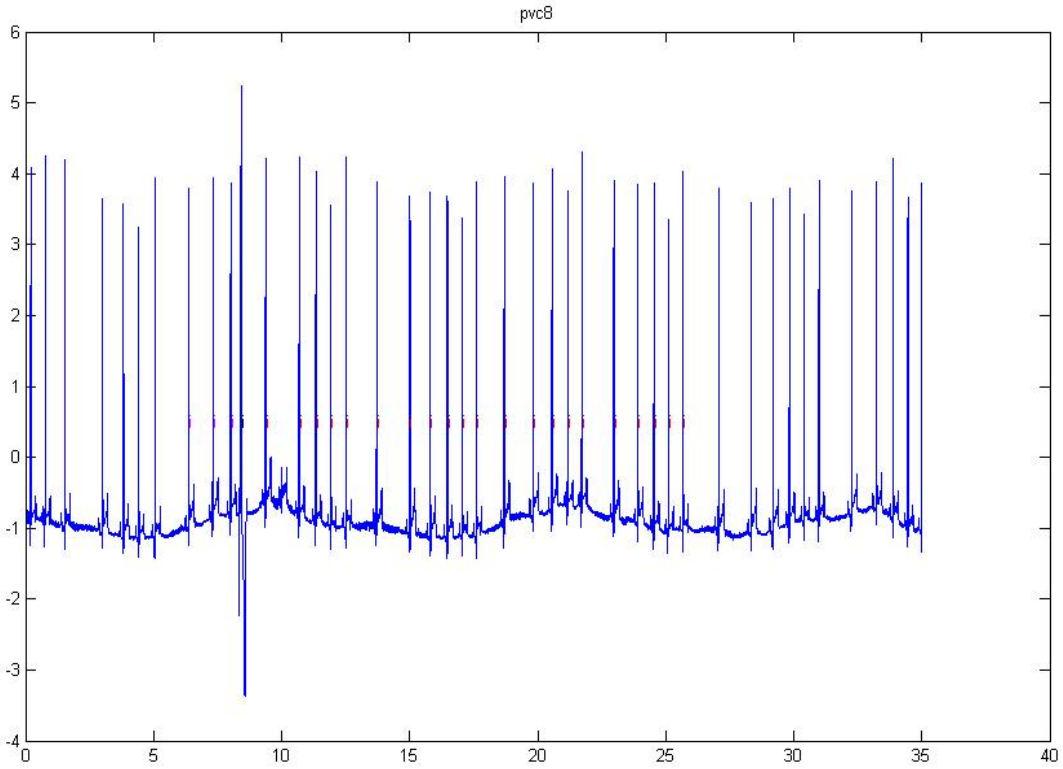

Figure 12 Losing a beat following the PVC

Since these "uncaptured" beats were not a regular aspect of naturally occurring PVCs, occasionally the data was reanalyzed without these data files.

6.3. Study limitations

Study limitations occurred in two phases, during data collection and then during data analysis.

6.3.1. Data collection

Infections were an issue. The first 2 canines suffered from infections due to the implant. The first only provided one data collection set. The second was able to complete the study despite the infection. To rectify this issue, a change was made to the equipment handling. One improvement was that the subcutaneous leads were coated with fastpass lubricious coating prior to sterilization. Additionally, they were soaked in solution of

antiseptic (Chlorhexidine Gluconate) and wide spectrum antibiotic (Enrofloxacin) prior to implant. These updates to the process resulted in the prevention of further infections.

Since the author of the study was not collecting the data, the HRT Data Collections Study Plan had to be enhanced for clarity after the data collection had begun. The Study Plan did not request a minimum of 5 R-Waves be recorded prior to the PVC. This caused earlier data collection sessions to occasionally have too few events at the beginning of the file. Upon identification of the issue, the new requirement was requested of the data collector.

Other data collection process improvement would include ensuring that 20 PVC-free ventricular events occur before data was collected and used for the study. This would avoid the data collected from being altered due to HRT from previous events. As well, if the subject was distracted or anxious causing an erratic heart rate, the HRT data would not be collected until the heart rate had returned to a baseline.

6.3.2. Data analysis

Due to the high quality and quantity of data signals collected, the decision was made to complete the analysis of the data without using filters that might alter the raw data. Due to this decision, one data collection session (*Canine Two* 12/7/2004) was never analyzed due to the poor quality of the signal. It was left to be analyzed independently by creating separate tools to smooth the signal, but due to time constraints, it was simply not analyzed. Due to the large number of data collection sessions, this omission was considered acceptable.

As data files were being processes through Matlab as a part of a data collection session some files were removed from the analysis. The reason for the removal was either due to clinical or algorithm issues. Due to the large number (30) of data files collected at each data collection session, excluding a few files was not an issue. A suggested minimum of five files to be used was met by all data collection sessions.

There are a few clinical reasons in which a data file would be excluded in the analysis of the data collection session. The most obvious reason in which a file would be excluded would be if the clip did not contain the necessary signal; a single PVC with at least three R-waves prior and at least 21 R-Waves following the PVC. If a ventricular paced event were to occur during those events or immediately prior, than the data file would have to be removed. This is due to the paced event's ability to alter the current intrinsic rate. Another reason would be if the occurrence of noise so that R-waves could not distinguished.

As mentioned previously, an anomaly occurred after some PVCs where the CP was delayed by one, two or three intervals. This condition had the potential to cause the averaged data to show a lack of HRT when HRT may have occurred. These occurrences were marked were noted during analysis, and on numerous occasions the data was analyzed with and without the data files with these events.

Algorithm issues occurred due to the limitations of the analysis tools. All algorithm rejected files were due to the fact that a single set of trims were defined for an entire data collection session and that in most cases, not all data files could conform to a single set up and work correctly. The most common result of this set-up was over-sensing and under-sensing of R-Waves or the PVC complex itself. Double-counting the different

peaks of the PVC as R-Waves occurred in some files, while other files missed counting pre-PVC R-waves because of their closeness to the PVC.

6.4. Potential uses

Determining that canines have HRT is very simple, yet powerful knowledge. As HRT continues to be analyzed as a risk factor for different cardiac disease states, further research can be done in the lab that is not possible through chronic patient studies involving Holter monitors.

Over the years, implantable cardiac devices have matured and become more sophisticated. Instead of blindly delivering therapy when the heart rate increases, these devices attempt to assess the patient's physical state based on other factors in conjunction with heart rate. This has increased the number of disease states it can treat therefore increasing the possible patient population of the devices.

With the medical community's excitement over new generation "smart" devices which provide a lot more diagnostics and therapy options, HRT may be used to provide additional information to the physician on the patient's disease progression.

Class III cardiac medical devices such as pacemakers, ICD and Cardiac Resynchronization Therapy Defibrillators (CRT-D) frequent use canines in the lab to mimic the human heart model. These devices also have all the data have the data required to calculate HRT. Their PVC algorithms identify the occurrence of a PVC and software could be added to maintain pre-peaks and store the post-peak information. An example usage of this data would be to collect HRT information and then displayed as trends for the physician in order to monitor disease progression. Once proven in devices, this stratifier could potential be used to identify

the potential for Myocardial Infarction or hospitalization. If HRT becomes a proven indicator of an onset of heart complications within cardiac patient, devices could be enhanced to notify the patients of a complication of the HRT indicators hit a threshold or change substantially for the worse. Most implantable cardiac devices have a patient notify technology built in which gets the patient's attention through vibration or sound to advise them to seek immediate medical attention.

Adding a new risk factor such as HRT to medical devices would not be a simple task. It would require a lot more research to determine the accuracy as well as the need of such information. A first obvious challenge would be to determine an algorithm to avoid invalid data swayed by other factors such as HRV.

6.5. Future Research

Determining that canines have HRT is only the beginning of this research topic. Further characterizing HRT in canine would be interesting. Are the current cutoffs for humans zero for TO and 2.5 ms/RR interval for TS ideal for animals? Also consider, do the same results found in subsequent HRT research also apply to canines? For example, research was performed which imply that the size of the Coupling Interval of the PVC compared to the base rate does not affect the values of the patient's HRT quantifiers. Is this the same for canines? Another topic would be to research the comparison of the impact of different medication on the TS and TO for humans versus canines. Due to the results of this study, considering the correlation of HRV and HRT would be interesting.

Future canine research should monitor naturally occurring PVCs. In order to aid the quality of future analysis, full medical histories and all medications used prior to and during the data collection should be recorded for each subject.

7. Conclusion

The data collected as a part of this study shows that canines display HRT. The following figure displays a summary of the 22 data collection sessions[14] where medication was not involved. For each interval the range of interval durations are noted through vertical lines. The summary data (reflected by the "Mean" line) has both a Turbulence Onset (-0.089) and Turbulence Slope (69.148ms/beat) which imply the presence of HRT.

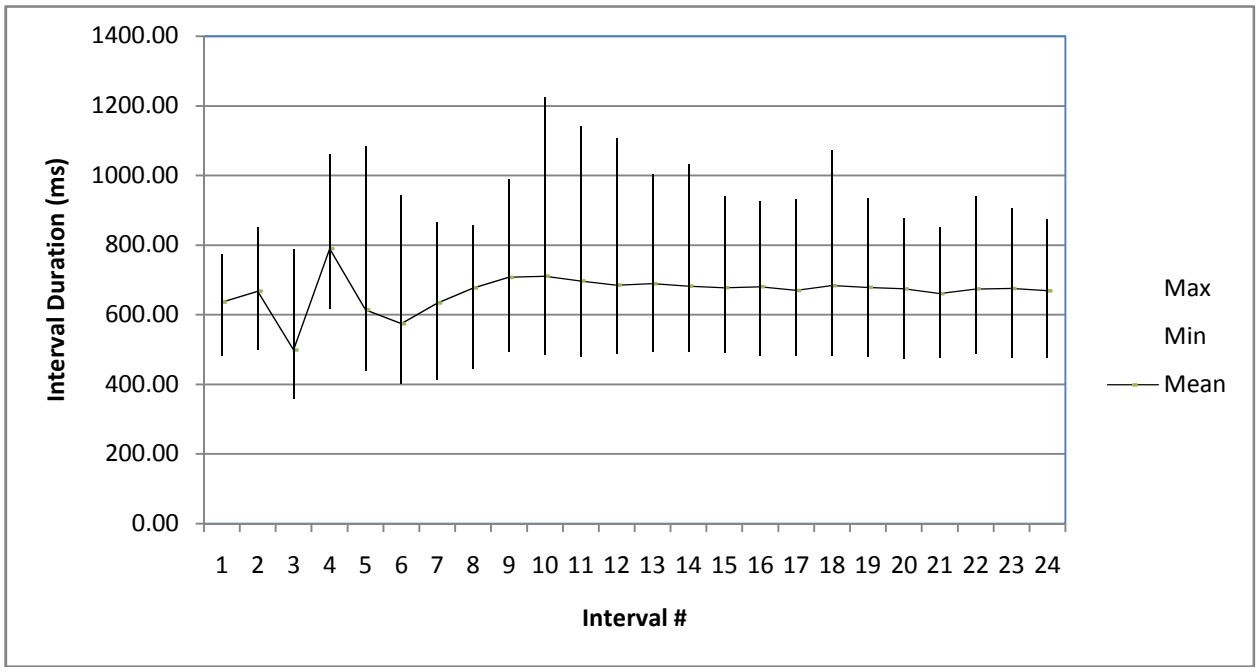

Figure 13 Mean Heart-Rate Data (non-medicated)

Such discoveries are important in today's medical device field. Implantable cardiac device technology has matured from devices which blindly delivered therapy to devices which try to improve the intelligence of the devices such so that therapy make specificity and sensitivity 100%

[14] Average data from the following sessions was then combined by determining the mean, minimum and maximum length of each interval: Canine One, results 1; Canine Two, 01/25/05; Canine Two, 10/21/04, results 3; Canine Two, 11/01/04, result 2; Canine Two, 12/21/04, result 2; Canine Three, 01/04/05; Canine Three, 01/25/05; Canine Three, 02/08/05; Canine Three, 02/15/05; Canine Four, 09/21/04; Canine Four, 09/27/04, result 2; Canine Four, 10/07/04; Canine Four, 10/13/04; Canine Four, 10/21/04; Canine Four, 10/26/04; Canine Four, 11/01/04; Canine Four, 12/21/04; Canine Five, 01/04/05; Canine Five, 01/25/05, result 2; Canine Five, 02/15/05, result 2; Canine Five, 03/08/05, result 2; Canine Five, 03/29/05, where results reflects which run in Appendix D – Raw Data Analysis Results was used in the case that multiple analysis were run.

accurate. Absence of as well as a reduced HRT is a potential indicator of the existence and progression of several types of heart disease which lead to SCD and mortality. Knowing that canines have HRT following a single PVC allows the potential of using this risk factor in different therapy options while continuing to test them on the known canine cardiac model.

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US Food and Drug Administration www.fda.gov

Appendix A – Study Plan

HRT DATA COLLECTION
STUDY PLAN for 08/17/2004

Using the set-up required for the Sputnik Study 428. Assumptions are the following:

1. For this portion of the data collection, the ECG lead II, RA and RV are compulsorily, but data will be collected from all channels due to its availability.
2. It is possible to collect at least 30 seconds worth of signal data.
3. It is possible to stabilize the dog so he is stationary during the data collection.

The following steps will be performed for each test case:

1. Turn On DAQ with the following channels:
    a. Channel 1 = EC1
    b. Channel 2 = ECII
    c. Channel 3 = RA
    d. Channel 4 = RV
    e. Channel 5 = ECG I
    f. Channel 6 = ECG II
    g. Channel 7 = ECG III
2. Set the RA of the PSA to Sense for the duration of the data collection.
3. Program the PSA to VOO pacing mode.
   Note: It is undesired to inhibit a paced pulse due to an R-wave since the attempt is to synchronize a pace and sensed event in order to cause a PVC.
4. Start Pacing the PSA at 30 bpm (2 second intervals).
5. Monitor for PVCs.
6. When a PVC is induced, immediately stop pacing by means of the PSA by switching the Ventricular channel of the Pace/Sense Switch Box to Sensing.
7. Monitor and record the signal for 25 R-Waves following the PVC.
    a. If no naturally occurring PVC happens within 25 intervals, stop recording and save the data.
    b. If a PVC occurs within the 20 intervals of the PSA generated PVC, restart counting R-Waves on the same recording. If another, natural PVC occurs within 20 R-Waves. That dataset is saved, but does not count towards the final valid data sets.
    c. If a PVC occurs within 20 and 25 R-Waves of the PSA generated PVC, the dataset is valid, but record for another 25 R-Waves in the attempt to get 2 cases in the same recording.
8. Document the content of every test case in the table below.

DATA COLLECTED DATE:

ADDITIONAL NOTES:

TEST CASE NUMBER	20 – 25 R-Waves following 1st PVC? (Yes / No)	2nd PVC? (Yes / No)	20 – 25 R-Waves following 2nd PVC? (Yes / No)	Notes
1				
2				
3				
4				
5				
6				
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Appendix B – Parent Study Plan

The following is an excerpt from the Parent Study of the HRT Data Collection Study.

Preoperative Procedure

The subject will be trained to go on a treadmill for several days prior to implant. The subject must be willing and able to run on the treadmill at the speeds of 5 mph, 10% grade, 6 mph, 10% grade and 7 mph, 5% grade. If most animals are not willing to perform this level of exercise, the speed will be reduced.
This will be a chronic procedure. The subject will be anesthetized according to BDP-301 using thiopental for induction and isofluorane for maintenance.

Implant Procedure

Study subjects will be anesthetized and prepared per BDP-302. The ventricular and atrial leads will be placed in the right ventricular apex and right atrial wall respectively. The subcutaneous electrodes will be placed under the skin. The locations of ECI and ECII vectors will be approximated on the canine using the human model, shown in Figure 1.

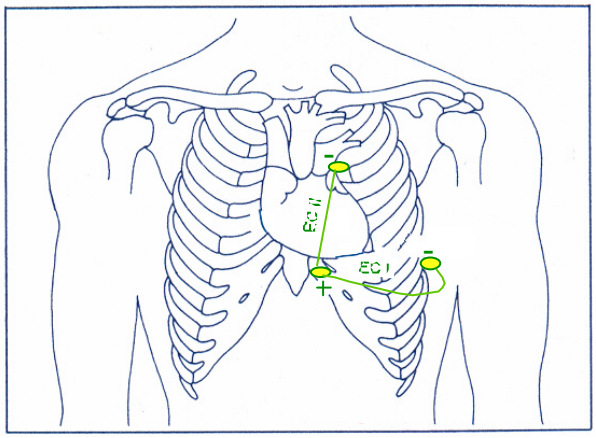
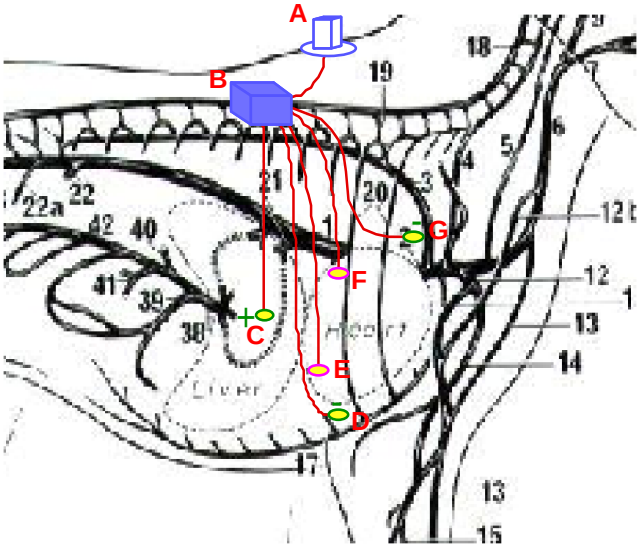


Figure 1.

The leads will be tunneled to the interscapular region and connected to an Epic HF header attached to a skin button. The lead attachments are shown in Figure 2.



A: Skin Button
B: Header
C: SVC Coil Lead: (+) EC I/II
D: SVC Coil Lead: (-) EC I
E: Ventricular Pacing Lead
F: Atrial Pacing Lead
G: SVC Coil Lead: (-) EC II

Figure 2.

Post-Operative Care

Post-operative surgical care will be provided per BDP-304. A bandage ± jacket will need to be maintained over the skin button throughout the duration of the study as long as necessary to ensure stability. The staff veterinarian will review the status of the implant site at weekly intervals.

Follow Up Data Collection

Data collection will be performed on day 21(±5) days, day 42(±5) days, day 65(±5) days, and day 90(±5) days. The following data will be collected from the subcutaneous leads. The duration of each data collection period will be 30 seconds. If exercise is being performed, the pacing rate will be a percentage above intrinsic rate (AIR) or a specific pacing rate, whichever is higher. In this case, the rate will be determined after animal runs on treadmill for 20 seconds (to allow the natural increase in heart rate). The percent value next to treadmill speed indicates grade level on the treadmill:

	Pacing	**Activity**
1	RV 10 % AIR or 160 bpm	5mph (10%)
2	RV 74x3 = 222 bpm	None
3	RA 10 % AIR or 160 bpm	4mph (10%)
4	RV 10 % AIR or 160 bpm	4mph (10%)
5	RA 20 % AIR or 222 bpm	6mph (10%)
6	RV 160 bpm	None
7	RA 10 % AIR or 160 bpm	6mph (10%)
8	RV 20 % AIR or 222 bpm	6mph (10%)
9	Induce AF	6mph (10%)
10	RV 20 % AIR or 222 bpm	4mph (10%)
11	RA 74x3 = 222 bpm	None
12	RV 20 % AIR or 222 bpm	5mph (10%)
13	Induce AF	None
14	Induce AF	4mph (10%)
15	None	6mph (10%)
16	RV 20 % AIR or 222 bpm	7mph (5%)
17	Induce AF	None
18	Induce AF	5mph (10%)
19	RA 20 % AIR or 222 bpm	4mph (10%)
20	None	None
21	Induce AF	7mph (5%)
22	RA 130 bpm	None
23	RV 10 % AIR or 160 bpm	6mph (10%)
24	RA 10 % AIR or 160 bpm	5mph (10%)
25	RV 130 bpm	None
26	RA 10 % AIR or 160 bpm	7mph (5%)
27	RA 20 % AIR or 222 bpm	5mph (10%)
28	None	4mph (10%)

	Pacing	Activity
29	None	None
30	RA 20 % AIR or 222 bpm	7mph (5%)
31	RV 10 % AIR or 160 bpm	7mph (5%)
32	RA 160 bpm	None
33	None	5mph (10%)
34	None	7mph (5%)

During the first study, the activity level – speed and percent grade, may be adjusted such that myopotential signal is clearly visible without danger to the animal. The dog will rest between data collection sessions involving physical activity for approximately 2 minutes, or as recommended by the veterinarian.

On the last day of the study, before explant, additional data will be collected after the animal has been anesthetized. Two sets of the following data will be collected from the subcutaneous leads, while pacing through the RV lead.

In addition, VF will be induced (less than five times) and data collected prior to the rescue shock.

Pacing	Activity
None	None
RV 130 bpm	None
RV 160 bpm	None
RV 3x74 = 222 bpm	None
Induce VF	None
Induce VF	None
None	None

Study Duration

The study duration will be 90(±5) days for each animal.

Explant Procedure

Animals shall be anesthetized per BDP-301. Following the acquisition of data (see Section 10.4) at the last time point of the study period, the animals are to be anticoagulated and humanely euthanized per BDP-307 by an Animal Health Technician. The model 1488T leads (both in RA and RV) shall be carefully exposed and dissected from the surrounding tissue. The subcutaneous leads shall be exposed, examined and photographed. Any remarkable items will be noted in the animal data records.

Appendix C – Data Analysis Software

The following functions provide the project specific Matlab code used to automate the data analysis.

processSession()

```
function []=processSession()
    % Create trims:
    % 1 = number of channel to use:
    trims(1) = 5;
    % 2 = using negative data stream:
    trims(2) = true;
    % 3 = pre-PVC delay
    trims(3) = 30;
    % 4 = post-PVC delay
    trims(4) = 320;
    % 5 = multiplication value for std dev of threshold calculation:
    trims(5) = 2.4;
    % 6 = use inverse of data for the pvc:
    trims(6) = false;
    % 7 = points in each direction that you look for the pvc peak when you
    % use a different orientation of the data for pvc versus peaks:
    trims(7) = 70;
    % 8 = Number of points to ignore at the beginning if the highest peak
    % appears there.  This is due to a spike that is sometimes seen at the
    % beginning of the complex (default 25):
    trims(8) = 35;
    % 9 = number of files
    trims(9) = 30;

    % Number of files to process:
    %numFiles = input('How many files are there to process in this directory? ','s');
    numFiles = trims(9);
    if isempty(numFiles)
        numFiles=0;
    else
        % Prompt user to provide file:
        [file,path,filt]=uigetfile('*.*','Where is the pvc1 to process?');
        name = 'pvc';
        % numFiles=str2num(numFiles);

        % Matrix holds all the data involving cycle lengths for this session:
        cycleLengths = zeros(numFiles,24);
        % Matrix holds all the data involving indices for this session:
        indices = zeros(numFiles,25);

        % Process each file in the session:
        H=200;
        figure(H);
        for i=1:numFiles
            file = strcat(name,num2str(i));
            disp('Opening...');
            disp(file);
            fid=fopen([path,file],'rb','b');
            if fid<0
                disp('Skipping.  No such file.');
                %save summary cycleLengths indices
                %error('No such file');
                %error(file);
            else
                [CLs,indVector] = readdata(path,fid,H,i,trims);
                H=H+1;
                % Copy over the indices and cycle Lengths:
                for j=1:(length(indVector))
                    indices(i,j)=indVector(j);
                end
                for j=1:(length(CLs))
                    cycleLengths(i,j)=CLs(j);
                end
```

```
    end

end

% Remove any rows that start or end with a zero.
% Find a row with a zero, delete it, search again.
[numrow,numcol]=size(indices);
delRow = zeros(numrow);
disp('Of ');
disp(numrow);
disp('entries, delete');
rowsToDelete=0;
for j=1:numrow
    if ((indices(j,1)==0) || (indices(j,numcol)==0))
        rowsToDelete=rowsToDelete+1;
    end
end
disp(rowsToDelete);
if rowsToDelete>0
% Go through again and delete the rows (one per pass):
    foundZeros=1;
    while (foundZeros)
        rowToDelete=-1;
        for j=1:numrow
            if ((indices(j,1)==0) || (indices(j,numcol)==0))
                % Record the row to delete:
                rowToDelete=j;
            end
        end
        disp('rowToDelete:');
        disp(rowToDelete);
        if (rowToDelete == -1)
            % No more rows to process:
            foundZeros=0;
        else
            rowsToDelete=rowsToDelete-1;
            disp ('Removing row');
            disp (rowToDelete);
            disp ('Contains of row:');
            disp (indices(rowToDelete,:));
            % Removing Row:
            indices(rowToDelete,:) = [];
            % Recount the number of rows:
            [numrow,numcol]=size(indices);
        end
    end
end
% Test for sanity:
if (rowsToDelete ~= 0)
    disp('rowsToDelete SHOULD BE ZERO BUT WAS:');
    disp(rowsToDelete);
end
% Find the data set that represents the average data:
avgIndices = zeros(1,numcol);
for i=1:numcol
    % For each position, calculate the average:
    avgIndices(i)=mean(indices(:,i));
end

% Calculate the resulting R-R intervals:
avgRRIntervals = diff(avgIndices);

% Calculate the pre intervals:
RRneg2 = avgRRIntervals(1);
RRneg1 = avgRRIntervals(2);
% Coupling interval:
ci = avgRRIntervals(3);
% Compensatory Pause after VPB:
cp = avgRRIntervals(4);
RR1 = avgRRIntervals(5);
RR2 = avgRRIntervals(6);
```

```
        % Turbulence onset:
        TO = ((RR1 + RR2) - (RRneg2 + RRneg1)) / (RRneg2 + RRneg1);

        % Handling Turbulence Slope:
        % Calculate the slope of each set of 5 consecutive events and store it in
        % an array:
        for i=5:(length(avgRRIntervals)-5)
            Y=avgRRIntervals(i:i+4);
            X=[i:i+4];
            SPxy=SUMofPRD(X,Y);
            SSx=SUMofSQ(X);
            slopeResults(i-4)=SPxy/SSx;
        end
        [maxslopevalue,maxslopeindex]=max(slopeResults);
        [minslopevalue,minslopeindex]=min(slopeResults);
        medianslopevalue=median(slopeResults);
        meanslopevalue=mean(slopeResults);

        % Save when you have processed all the files:
        currentDir=cd;
        cd(path);
        cd('results');
        summary_file = 'summary'
        save( [summary_file], 'trims', 'avgRRIntervals', 'RRneg2', 'RRneg1', 'ci', 'cp', 'RR1',
'RR2', 'TO', 'slopeResults', 'maxslopevalue', 'maxslopeindex', 'minslopevalue', 'minslopeindex',
'medianslopevalue', 'meanslopevalue', 'indices');

        % Plot the cycle lengths:
        figure(100)
%        subplot(2,1,2)
%        subplot(1,1,1)
        plot(avgRRIntervals,'-*')
        ylabel('Cycle Length (ms)')
        xlabel('Interval #')
        % SAVE FIGURE:
        hgsave('summary.fig');
    end
```

viewData()

```
%For plotting purposes, div determines into how many portions to divide the
%data
div=1;
warning off

%Channels indicates which channels you would like to plot.
%1 = ECI
%2 = ECII
%3 = RA
%4 = RV
%5 = ECGG
%6 = ECGI
%7 = ECGII
channels=[1,2,3,4,5,6,7];
%channels=[1,2,3,4,5];

[file,path,filt]=uigetfile('*.*','Choose File To Open');
fid=fopen([path file],'rb','b');
if fid<0
    error('Invalid File Name')
end

len=fread(fid,1,'int32');
h1len=fread(fid,1,'int32');
VirtualChannels =(char(fread(fid,h1len,'uchar')))';


hour = fread(fid,1,'int32');
minute = fread(fid,1,'int32');
if minute < 10,
    data.time = [int2str(hour),':0',int2str(minute)];
else,
    data.time = [int2str(hour),':',int2str(minute)];
end;
month = fread(fid,1,'int32');
day = fread(fid,1,'int32');
year = fread(fid,1,'int32');
data.date = [int2str(month),'-',int2str(day),'-',int2str(year)];
filedate=data.date;

ScanRate=fread(fid,1,'float32')
InterChannelDelay=fread(fid,1,'float32');

headerlen=fread(fid,1,'int32');

UserHeader=char(fread(fid,headerlen,'uchar'));
Header=UserHeader'
d=fread(fid,[8 inf],'int16');
fclose(fid);

d=d*10/(2^12);  % 12bit data acquisition card
d=d/500;        % gain was set at 500
d=d*1000;       % convert V to mV

d(1:2,:)=d(1:2,:);
%dfilt=d;
%d=[];
%e=firfilt(dfilt(6,:),ScanRate,45,4*ScanRate,'low');
%d=dfilt(:,1:length(e));
%d(6,:)=e';
Size=size(d);
range=1:Size(2);
x=(range)/ScanRate;
lr=length(range);

labels={'ECI','ECII','RA','RV','ECGG','ECGI','ECGII','Noise'};
lchan=length(channels);
```

```
for i=1:div
a=ceil((i-1)*lr/div+1);
b=floor(i*lr/div);
    for j=1:lchan
        figure(i+div);
        subplot(lchan,1,j)
        plot(x(a:b),d(channels(j),range(a:b)))
        ylabel([char(labels(channels(j))) ' mV'])
        xlim([x(floor(a)) x(ceil(b))]);
        amp=abs(max(d(channels(j),range(a:b)))-min(d(channels(j),range(a:b))));
        ylim([min(d(channels(j),range(a:b)))-.05*amp max(d(channels(j),range(a:b)))+.05*amp]);
        grid on
        if channels(j)==1
           title([path file])
        elseif j==lchan
           xlabel ('Time (s)')
        end
   end
orient portrait
end
```

readData()

```
function [CLs,indVector]=readdata(path,fid,H,fileN,trims)

%For plotting purposes, div determines into how many portions to divide the
%data
div=1;
warning off

%Channels indicates which channels you would like to plot.
%1 = ECI
%2 = ECII
%3 = RA
%4 = RV
%5 = ECGG
%6 = ECGI
%7 = ECGII
channels=[1,2,3,4,5,6,7];
%channels=[1,2,3,4,5];

len=fread(fid,1,'int32');
h1len=fread(fid,1,'int32');
VirtualChannels =(char(fread(fid,h1len,'uchar')))';


hour = fread(fid,1,'int32');
minute = fread(fid,1,'int32');
if minute < 10,
    data.time = [int2str(hour),':0',int2str(minute)];
else,
    data.time = [int2str(hour),':',int2str(minute)];
end;
month = fread(fid,1,'int32');
day = fread(fid,1,'int32');
year = fread(fid,1,'int32');
data.date = [int2str(month),'-',int2str(day),'-',int2str(year)];
filedate=data.date;

ScanRate=fread(fid,1,'float32')
InterChannelDelay=fread(fid,1,'float32');

headerlen=fread(fid,1,'int32');

UserHeader=char(fread(fid,headerlen,'uchar'));
Header=UserHeader'
d=fread(fid,[8 inf],'int16');
fclose(fid);

d=d*10/(2^12);  % 12bit data acquisition card
d=d/500;        % gain was set at 500
d=d*1000;       % convert V to mV
d(1:2,:)=d(1:2,:);
Size=size(d);
range=1:Size(2);
x=(range)/ScanRate;
lr=length(range);

labels={'ECI','ECII','RA','RV','ECGG','ECGI','ECGII','Noise'};
lchan=length(channels);

% Returns cycle lengths and the indices for this file:
[CLs,indVector] = HRTpeaks(path,d(trims(1),:),ScanRate,H,fileN,trims)
```

HRTPeaks()

```
function[CLs,indVector]=HRTpeaks(path,signal,fs,H,fileN,trims)
% Where to display the markers (Y-axis value):
ydispvalue = 0.75;

%Plot the original signal:
figure(H)
subplot(1,1,1)
plot((1:length(signal))./fs,signal);
fileName=['pvc' num2str(fileN)];
title(fileName);

% Interpret some of the trims (whether to use the max peak of the inverse
% of the data for detecting the peaks and PVC):
signOfPVC = 1;
if (trims(6))
    signOfPVC = -1;
end
signOfData = 1;
if (trims(2))
    signOfData = -1;
end
% Find the largest peak (of the positive peaks):
%   Note:  There is sometimes a peak in the signal at the beginning of the
%   recording which throws off the PVC detection.  If the PVC is detected
%   in the first 5 data points, ignore it, and pick the next highest (but
%   print out a message that the spike existed.
%let the threshold for peak detection be mean of the data + X * standard
%deviation
thresh=trims(5)*std(signOfData * signal) + mean(signOfData * signal);
[maxvalue,pvcIndex]=max(signOfPVC * signal);

if pvcIndex<trims(8)
    [tempmaxvalue,temppvcIndex]=max(signal((trims(8)+1):length(signal)));
    pvcIndex=temppvcIndex+trims(8);
    disp('Spike occurred in the first 25 data points collected');
    thresh=trims(5)*std(signOfData * signal((trims(8)+1):length(signal))) + mean(signOfData *
signal(26:length(signal)));
end

%  Find the peak associated with the PVC, which is the same orientation as
%  the other peaks being detected:
if (signOfPVC ~= signOfData)
    disp(pvcIndex);
    [realPVCValue,realPVCIndex] = max(signOfData * signal((pvcIndex-
trims(7)):(pvcIndex+trims(7))))
    pvcIndex = (pvcIndex-trims(7)) + realPVCIndex;
    if (realPVCIndex == 1)
        disp('*****************************');
        disp('The pvc index was potentially at the incorrect space.');
    end
    disp('Recalibrated the PVC');
end

% Time before and after a PVC in while you are not interested in an R-Wave (Avoids
% double detection of the PVC):
%  "trims" used so this can vary:
prePVCdelay=trims(3);
postPVCdelay=trims(4);

% Take only the signal that follows the PVC (+25 is so that you don't double
% count the PVC.
AfterPVC=signal(pvcIndex+postPVCdelay:end);

% Get the peaks after the PVC:
% Note:  Even though PVC max is best calculated on positive peak, the
% R-waves are best determined by the negative peaks.
disp('postInd processing');
postInd=getPeaks((signOfData * AfterPVC),thresh,trims);
```

```
% Get the peaks before the PVC:
preInd=getPeaks((signOfData * (signal(1:(pvcIndex-prePVCdelay)))),thresh,trims);

% Create an array of R-waves where the 4th index is the PVC:
%   Note:  If there is not enough pre R-Waves mark the indexes with zero, and
%   print a message!  Peaks in the first 10 have been ignore, so zero
%   represents "no value" well.
% Vector that will be returned:
indVector=zeros(1,25);
% Fill in the pre R-Waves in indexes 1 to 3:
if (length(preInd)==0)
    disp('Warning: There is no pre-PVC R-Waves defined.');
else
    tempIndex=0;
    if ((length(preInd)- 3) < 0)
        disp('Warning: There are only');
        disp(length(preInd));
        disp('Pre R-Waves');
    end
    while ((tempIndex < 3) && ((length(preInd)-tempIndex) ~= 0))
        indVector(3-tempIndex)=preInd(end-tempIndex);
        tempIndex=tempIndex+1;
    end
end
% Fill in the PVC in index 4:
indVector(4)=pvcIndex;
% Fill in the post R-Waves:
tempIndex=5;
while ((tempIndex <= length(indVector)) &&(tempIndex <= (length(postInd))))
    indVector(tempIndex)=(pvcIndex + postPVCdelay + (postInd(tempIndex-4)));
    tempIndex = tempIndex + 1;
end

% Display marks to show the events recorded:
%   Mark the PVC in black.
%   2nd value (where to display marks) is .75 usually.
text(indVector(4)./fs,ydispvalue,'i','Color','black');
%   Mark the post PVC R-Waves in red:
text((indVector(5:end))./fs,(ones(1,(length(indVector(5:end)))).*(ydispvalue)),'i','Color','red')
;
%   Mark the pre-PVC R-Waves in magenta:
text((indVector(1:3))./fs,(ones(1,3)).*(ydispvalue),'i','Color','magenta');

% SAVE FIGURE:
%  Firstly, save where you are:
currentPath = cd;
%  7 - directory exist by that name:
cd(path);
if (exist('results') ~= 7)
    mkdir ('results')
end
cd ('results');
hgsave(fileName);
cd(currentPath);

% CYCLE LENGTHS:
% Calculate cycle lengths by taking differences between consecutive R-wave
% locations and convert to ms
CLs=1000*diff(indVector)./fs;
% Account for any zero values in indVector:
% PRE-PEAKS:
index=1;
while (indVector(index)==0)
    % If the value in the peak array is zero, zero it in the cycle lengths
    CLs(index)=0;
    index=index+1;
end
% END-PEAKS:
index=length(indVector);
while (indVector(index)==0)
```

```
    % If the value in the peak array is zero, zero it in the cycle lengths
    CLs(index)=0;
    index=index-1;
end
```

getPeaks()

```
function ind=getPeaks(data,thresh,trims)
boundary=25;
%find all the data points that are greater than the threshold
crossThresPoints=find(data>thresh);
%take the difference between all the data points found above.  The
%difference between adjacent points should equal one.
d=diff(crossThresPoints);

%find the difference above greater than 25
e=find(d>boundary);

%peak "humps" should end at the points found above
peaka=crossThresPoints(e);
start=1;

%go through each "hump" and find the maximum.  Write each location of the
%max into a vector called ind.
if (length(peaka) == 0)
    disp('There are no peaks that passed the threshold');
    ind=[];
else
    for i=start:length(peaka)
        if peaka(i)-80<=0
            disp('Peak too close to start');
            disp(peaka(i)-80);
        else
            [height(i-start+1),temp]=max(data((peaka(i)-80):peaka(i)));
            ind(i-start+1)=peaka(i)-81+temp;
        end
    end
end
```

SUMofPRD()

```
function SPxy=SUMofPRD(X,Y);
Xavg=mean(X);
Yavg=mean(Y);
sum=0;
for i=1:length(X)
    d=(X(i)-Xavg)*(Y(i)-Yavg);
    sum= sum + d;
end;
SPxy=sum;
```

SUMofSQ()

```
function SSx=SUMofSQ(X);
Xavg=mean(X);
sum=0;
for i=1:length(X)
    d=(X(i)-Xavg)^2;
    sum= sum + d;
end;
SSx=sum;
```

Appendix D – Raw Data Analysis Results

Legend	
Cell Color	**Values of HRT averaged values**
	As expected for HRT
	Use of algorithm was not ideal. Rerun of data collection session to better capture data.
	Not as expected for HRT, but session was analyzed and values are reflective.
	Not as expected for HRT, but session was rerun from another perspective.
	Session was not analyzed due to quality of data.

SUBJECT		REPRODUCTION DETAILS										HRT averaged values						Turbulence Onset	SLOPE						NOTES	
Subject	**Date**	**Numbers of files used**	**Channel Number Used Trims(1)**	**Negative Data Stream? Trims(2)**	**Pre-PVC blanking period Trims(3)**	**Post-PVC blanking period Trims(4)**	**Multiplication value for Std Dev of Threshold Trims(5)**	**Use of Inverse Data for the PVC? Trims(6)**	**Look for a PVC in each direction, when data & PVC is of opposite polarity Trim(7)**	**Duration to ignore peaks at the beginning of file Trim(8)**	**number of files Trim(9)**	**RR-2**	**RR-1**	**Coupling Interval**	**Compensatory Pause after VPB**	**RR1**	**RR2**	**Turbulence Onset**	**Max Slope Index**	**Max Slope**	**Min Slope Index**	**Min Slope**	**Median Slope**	**Mean Slope**	**Files that were removed**	**Additional Notes**
Canine One	9/1/2004	11	7	TRUE	0	320	2.19	FALSE	70	35	30	732.0909	701.1818	494.0909	723.0909	663.8182	622.4545	-0.1026	8	9.7727	15	-15.8182	-0.5273	-1.2273	1,2,3,5,6,7, 10,13,17 - 22,24,28 -30 (note pvc12 doesn't exist)	**bad algo:** **wrong pvc:** 1,3,6,10,13,19,20, 21,24,28,29,30 **missing evt:** 7 **extra pre:** 5 **bad data:** **no pvc:** 2 **look at:** 27 **NOTE:** pvc12 doesn't exist seems like there is no CP.
		11	7	TRUE	0	320	2.19	FALSE	120	35	30	732.0909	701.1818	494.1818	723.0000	663.8182	622.4545	-0.1026	8	9.7727	15	-15.8182	-0.5273	-1.2273		**modified PVC detection through trims**
Canine Two	1/25/2005	19	5	TRUE	50	320	3.50	TRUE	70	35	30	696.8947	638.2105	531.4211	803.7368	595.4211	591.4737	-0.1110	2	29.1632	5	-21.9737	-0.3000	1.7400	7,29,23,20, 12,11, 1,2,3,22, 24	**bad algo:** **pre:** 7,29 **wrong pvc:** 11,12,20,23 **bad data:** 24 – no pvc 2,22 - paced pre 3 - 2 pvcs 1 - (-3) **interesting:** +1: 15,30, +3: 14
Canine Two	10/21/2004	9	2	FALSE	25	320	2.19	TRUE	70	35	30	504.4444	525.1111	545.0000	854.4444	629.1111	478.7778	0.0761	9	37.4889	12	-41.9778	6.6889	2.4874	1,2,5,8,9, 10,12,14, 15,16, 18,19,20, 22-29	**Note from lab:** was jumpy control1 and first 10 records maybe off **bad data:** **noise:** 10,28 **2 pvcs:** 23,26 **algo:** **undersensing:** 4,8,9,14,16,20,22,27 **oversensing:** 1,2,5, 15,24, 25 **missed pre:** 12,18,19
		12	2	FALSE	0	350	2.19	TRUE	120	35	30	497.1667	574.1667	568.6667	791.0000	539.7500	476.0000	-0.0519	2	42.2500	6	-26.5333	6.4083	4.6128	1,8-10, 12-16, 18-23, 26-28	**Improved PVC detection through trims.** **Undersensing:** 8,9,14,15, 16, 18,20,22,27 pacing too close: 12,21,23,26 odd events at +1 or +2: 1,10,13,19 noise: 28
		9	2	FALSE	0	350	2.19	TRUE	120	35	30	519.4444	582.5556	585.6667	778.8889	580.8889	484.8889	-0.0329	2	47.7778	6	-32.3556	5.9778	4.5333	1,4,7-10, 12-24,26-28	Improved PVC detection through trims. Removed 3 files that had paced event immediately prior. Undersensing: 8,9,14,15, 16, 18,20,22,27 pacing too close: **4,7,17,**12,21,23,26 odd events at +1 or +2: 1,10,13,19 noise: 28

SUBJECT		REPRODUCTION DETAILS										HRT averaged values						Turbulence Onset	SLOPE						NOTES	
Subject	Date	Numbers of files used	Channel Number Used Trims(1)	Negative Data Stream? Trims(2)	Pre-PVC blanking period Trims(3)	Post-PVC blanking period Trims(4)	Multiplication value for Std Dev of Threshold Trims(5)	Use of Inverse Data for the PVC? Trims(6)	Look for a PVC in each direction, when data & PVC is of opposite polarity Trim(7)	Duration to ignore peaks at the beginning of file Trim(8)	number of files Trim(9)	RR-2	RR-1	Coupling Interval	Compensatory Pause after VPB	RR1	RR2	Turbulence Onset	Max Slope Index	Max Slope	Min Slope Index	Min Slope	Median Slope	Mean Slope	Files that were removed	Additional Notes
Canine Two	10/26/2004	20	5	TRUE	30	320	2.40	FALSE	70	35	30	677.5500	697.3000	490.3000	873.0000	566.6000	706.4000	-0.0741	1	61.9950	5	-42.6400	-2.7600	2.9283	1,2,4,7,9, 10,13,15, 24	**bad data - paced on pre:** 7 **look at:** 22,23 Notes: 22 +1 odd morphology 19,20, ex of pvc having affect but not expected There's an odd pause after some pvcs +3 ex: 18,22,16,11
		13	5	TRUE	30	320	2.40	FALSE	70	35	30	691.2308	717.4615	495.6154	850.0000	583.8462	661.5385	-0.1159	1	55.7462	5	-43.4154	-1.5000	6.0744	1,2,4,7,9, 10,13,15, 24 plus 16,22,26, 23,8, 11, 19,27	**Same as other run except removed** 23,8,11,19,27 due to pre-pace 16,22,26 +1 morphology
Canine Two	11/1/2004	13	2	FALSE	28	320	2.10	TRUE	70	35	30	611.3077	668.9231	467.0769	842.9231	573.0769	532.2308	-0.1366	2	36.7000	5	-17.2538	5.1538	5.9421	1,4,5,6,1 0, 11,12,16, 18,20,22, 25-30	**Look at:** 13,15,17 **oversensing:** 4,5,20,22, 27,29,30 **undersensing:** 6,26 **missed -1:** 1,11,16,18,25 **extra -1:** 10 **wrong PVC:** 2,8 **NON ALGO:** **don't understand:**12
		15	2	FALSE	26	320	2.40	TRUE	70	35	30	633.2000	667.2000	475.8000	842.8667	561.9333	530.3333	-0.1601	1	33.5333	14	-20.1733	5.1467	5.2431	1,2,4,6,1 0, 11,14 16,22,25 -30	**undersensing:** 6,26,27,30 **extra -1:** 1,2,10,14,25 **wrong PVC:** 22 **missed -1:** 4,11,16 **oversense:** 29 **no pvc:** 28
Canine Two	12/7/2004																									Needs processing before I run algorithm
Canine Two	12/21/2004	27	5	TRUE	300	320	2.00	FALSE	70	35	30	771.8148	811.8148	818.2963	814.5926	712.1852	642.7037	-0.1444	2	58.5667	13	-34.3519	-5.0963	6.7884	1,6,20	record 1-21 was nervous and not calm **Algo:** wrong pvc: 6 missing pre: 1,20 **PVC incorrectly marked.**
		25	5	TRUE	70	320	2.00	FALSE	150	35	30	772.5200	810.7600	594.0800	1060.6000	723.4800	651.0800	-0.1318	2	58.1400	13	28.8600	-0.1400	7.0856	1,6,20,22 ,23	See other run. Also 22,23 due to pacing too close to pre events.
Canine Two	1/26/2005	18	1	TRUE	290	330	2.40	FALSE	70	35	30	693.0000	691.0556	790.3889	596.0000	679.2222	638.4444	-0.0480	2	14.2000	14	-0.4500	0.1000	2.1385	4,5,10-13,15,17, 22,26,27	Explant Algo - miss pre 10,26 Algo - bad filename -8 Odd beat - 4,5,11,12,15, 17,27 Extra paced - 13,22
Canine Three	1/4/2005	18	2	FALSE	30	320	2.40	TRUE	70	35	30	481.8889	498.8889	365.5556	617.1111	439.3889	400.3889	-0.1438	2	25.0444	9	-3.2889	1.0444	3.8926	1,4,5,6,7, 11,12,18, 21,23,28	**algo:** **wrong PVC:** 4,21,23,28 **wrong pre:** 7,17 **missed pre:** 11,12 **missed event:** 5,6,18 **bad data:** **2 pvcs:** 1
Canine Three	1/25/2005	30	2	FALSE	10	320	1.90	FALSE	70	35	30	546.7333	554.9667	406.0667	632.6667	550.9000	545.9667	-0.0044	3	16.9400	7	-8.2533	-0.3667	0.6171		Canine seems to be skipping beats. Look at 1, 5, 6, 7, 8, 13, 16, 19, 20, 25 **Note:** pvc9 double counted a beat, but it should affect the numbers since not in HRT equation.
		18	2	FALSE	10	320	1.90	FALSE	70	35	30	552.4444	561.0556	417.0000	647.6111	486.4444	470.0556	-0.1410	2	24.4222	7	-13.9111	2.4944	3.3107	1,5-7,9,13, 16,19, 24, 25, 27,30	Event between +1 and +2: 6,7,13,24,25,27 event between +2 and +3: 1,5,16,19,30 double count evt: 9 Note: pacing pre pvc in 4 and 30

SUBJECT		REPRODUCTION DETAILS										HRT averaged values						Turbulence Onset	SLOPE						NOTES	
Subject	**Date**	**Numbers of files used**	**Channel Number Used Trims(1)**	**Negative Data Stream? Trims(2)**	**Pre-PVC blanking period Trims(3)**	**Post-PVC blanking period Trims(4)**	**Multiplication value for Std Dev of Threshold Trims(5)**	**Use of Inverse Data for the PVC? Trims(6)**	**Look for a PVC in each direction, when data & PVC is of opposite polarity Trim(7)**	**Duration to ignore peaks at the beginning of file Trim(8)**	**number of files Trim(9)**	**RR-2**	**RR-1**	**Coupling Interval**	**Compensatory Pause after VPB**	**RR1**	**RR2**	**Turbulence Onset**	**Max Slope Index**	**Max Slope**	**Min Slope Index**	**Min Slope**	**Median Slope**	**Mean Slope**	**Files that were removed**	**Additional Notes**
Canine Three	2/8/2005	21	2	FALSE	35	320	2.50	FALSE	70	35	30	546.1905	542.9048	407.1429	642.8571	504.3333	473.0952	-0.1025	2	17.1667	9	-8.0330	4.6238	4.4463	4, 1, 2, 27, 21, 11, 10, 5, 3	**Algo:** 4: pre and PVC the same 1,2,27: missed pre **Clinical:** 5,10,11,21: how to handle PVC+3 3: how to handle PVC+2 **Note:** 26 used, but check out the long gap doesn't seem to be a PVC.
Canine Three	2/15/2005	25	2	FALSE	31	250	3.40	FALSE		25	30	587.4400	575.6000	423.2800	738.0400	538.0800	480.6400	-0.1241	2	33.3120	9	-12.2960	3.9000	6.8171	over or under sensing (have to control trim(3) - pvc3, pvc4, pvc6, pvc8 and pvc24	Check out pvc7-9, 13,16, 29 7 pulse deficit count
Canine Three	3/8/2005	15	2	TRUE	1	500	3.40	FALSE	70	35	30	999.7333	995.6667	640.2000	1000.6000	875.2000	995.6000	-0.0624	1	26.6467	7	-6.5200	1.2133	1.7920	1-4,6,10-12,14,17, 22,24-26, 28	Explant weird evt +1: 4,6,10,11,17,22 paced during pre: 2,3,12,14,24-2,.28 noisy signal 1
Canine Four	9/21/2004	9	2	TRUE	15	320	1.90	FALSE	70	25	30	530.2222	536.3333	359.2222	627.3333	494.0000	458.5560	-0.1069	2	34.3444	10	-16.7780	6.5111	5.7489		**Note from collector:** pvc23 - nervous about a fly **Data collection notes:** 1 - PVC? 2 – looks noisy.ooks noisy. 25,27 - watching low 4,6,7 - neg doesn't work, use positive 5,8,30 - oversensed pre 9 - missed 1st after PVC 11,12 - consider lower threshold 14,18,19 - missing pre 15,23 - 20 - pre missed, double a pre 21- pre missing, look at 1st post
Canine Four	9/27/2004	21	7	TRUE	1	320	2.20	FALSE	70	35	31	670.5714	709.4286	502.0000	794.3333	626.2381	604.0000	-0.1085	1	39.9190	4	-23.4524	-2.5190	1.5860	1,13-18,21, 25,30	**GENERAL** **bad data:** **pre is paced**- 18,15,17 **not enough pre** - 30 **2 pvcs** - 13,21 **algo:** **extra pre** - 1,14,16 **missed evt** - 25 **look @:** 11,29,31 **PASS 1 INCLUDED:** 2,10,12,20,24 (ignored pseudo events because not complete complex)
		16	7	TRUE	1	320	2.20	FALSE	70	35	31	676.0625	733.0000	516.8125	835.8125	582.2500	552.0625	-0.1950	1	45.2813	4	-16.3687	1.2000	4.4975	1,2,10,12-18, 20,21, 24,25,30	**PASS 1 EXCLUDED:** 2,10,12,20,24 because they had pseudo events following PVC
Canine Four	10/7/2004	24	6	TRUE	1	320	1.80	FALSE	70	35	30	633.7083	626.8750	417.4583	825.3333	565.6667	540.5000	-0.1225	2	27.7208	7	-8.7833	0.8833	4.2675	1,2,3,4,11, 26	**Never use:** 4 - pace after pvc **Algo:** pvc=1stPeak 2,3,11,26 wrong pvc 1 **Note (but used):** 18,19 have gap between +1 & +2 15 gap between +2 & +3 16 note +2
Canine Four	10/13/2004	17	2	TRUE	1	320	2.20	FALSE	70	35	30	673.5294	746.7647	476.3529	906.4118	639.8235	642.5294	-0.0971	1	36.1000	3	-23.5941	0.1529	0.4706	2,6,16,20-25, 27-30	**bad data:** pre=paced - 2,6,16,20,22,27,30 **bad algo:** pvc=pre - 21,23,24,25,28,29 **look at:** 11,15,17,28

SUBJECT		REPRODUCTION DETAILS										HRT averaged values						Turbulence Onset	SLOPE						NOTES	
Subject	**Date**	**Numbers of files used**	**Channel Number Used Trims(1)**	**Negative Data Stream? Trims(2)**	**Pre-PVC blanking period Trims(3)**	**Post-PVC blanking period Trims(4)**	**Multiplication value for Std Dev of Threshold Trims(5)**	**Use of Inverse Data for the PVC? Trims(6)**	**Look for a PVC in each direction, when data & PVC is of opposite polarity Trim(7)**	**Duration to ignore peaks at the beginning of file Trim(8)**	**number of files Trim(9)**	**RR-2**	**RR-1**	**Coupling Interval**	**Compensatory Pause after VPB**	**RR1**	**RR2**	**Turbulence Onset**	**Max Slope Index**	**Max Slope**	**Min Slope Index**	**Min Slope**	**Median Slope**	**Mean Slope**	**Files that were removed**	**Additional Notes**
Canine Four	10/21/2004	24	5	TRUE	25	320	2.19	FALSE	70	35	30	701.1304	769.4783	578.1739	766.6957	635.0870	698.3478	-0.0933	1	45.0435	7	-17.4174	-4.1913	1.2841	30,26,11, 5,2,1	**bad data:** 30 where is PVC? 26 paced in pre 11,5 - what is +2 **algo:** 2 missing pre 1 wrong pvc? **Look at:** 24 pace effect 16,12,10 pvc morph?
Canine Four	10/26/2004	29	2	TRUE	1	320	1.90	FALSE	70	35	30	530.2200	536.3300	359.2200	627.3300	494.0000	458.5600	-0.1069	2	34.3444	10	-16.7778	6.5111	5.7489	25	25 - double count for a paced event
Canine Four	11/1/2004	23	5	TRUE	25	320	1.80	FALSE	70	35	30	635.0870	752.2609	568.2174	878.8261	692.7826	634.8261	-0.0431	2	49.8391	6	-30.4739	1.2174	2.8061	4, 7, 10, 11, 15, 16, 22	**Algo:** 7,22 - wrong PVC 15,16 - double count PVC **Note (but used):** 1 - look at rate 21,24 - another evt? 9,28 - +2 **Note (but not used):** 10,11 - pace upset pre evt 4 - +2?
		18	5	TRUE	25	320	1.80	FALSE	70	35	30	635.7222	755.0000	542.3333	880.0000	624.0556	589.1667	-0.1276	2	76.4944	5	-48.8278	4.5667	6.3467	4,7,9, 10,11 15,16,19, 21,22,24, 28	This canine had a lot of base rate fluctuation. **Algo:** 7,22 - wrong PVC 15,16 - double count PVC **Not Used:** 10,11, 19 - pace pre pvc 4 - +2 - weird evt 9,28,21,24 - missed evt +2 **Note:** 25,23,17,14 - space between +1 and +2 very large. 13 - Great example of base rate fluctuation!
Canine Four	12/21/2004	27	2	TRUE	1	320	1.80	FALSE	70	35	30	653.7778	673.7407	412.6667	776.7037	597.3333	565.2222	-0.1243	1	40.9185	5	-12.8778	-2.0778	3.5415	1,19,27	1 – no pvc 19 - not enough pre 27 - noise **Look at (but included):** 17,22,11,6,5 (+1)
Canine Four	1/4/2005	9	1	TRUE	50	300	2.90	TRUE	70	35	15	521.2222	521.7778	403.7778	653.5556	518.5556	446.8889	-0.0744	2	15.4667	8	-0.6889	0.5333	1.8304	3,4,5,7,8, 10	Explant 3,4 - funny morph event 8 - extra pace 7 - wrong r-waves detect 5 missing pre-evt 10 - event odd
Canine Five	1/4/2005	16	2	FALSE	1	320	2.20	FALSE	70	35	30	534.9375	535.8125	421.3750	648.6875	485.2500	416.4375	-0.1579	2	32.7375	7	-11.7688	1.6000	4.1413	2,4,12, 15, 16, 17, 18, 19, 22, 23,26, 27,11	**bad algo:** **missed peak:** 3 **wrong pvc:** 2,4,12,15-19,22,23 **data?:** 11,26,27 **look at:** 1,3
Canine Five	1/25/2005	21	2	FALSE	1	320	2.20	FALSE	70	35	30	669.4762	715.0476	447.0952	796.8095	577.7143	576.0952	-0.1666	1	49.7619	4	-30.2571	0.5905	1.5749	1,6,8,11, 13,18,28	**General:** **wrong pvc -** 1,6,8,11,13,28,18 **missed pre -** 22 **bad data:** **pvc?** 14 **pass 1 includes 5,9,19 which have a 'missing' evt**
		18	2	FALSE	1	320	2.20	FALSE	70	35	30	686.6111	728.2222	435.1667	791.5556	534.0000	559.6667	-0.2270	1	68.7667	4	-37.7111	-0.1833	2.6496	1,5,6,8, 9,11,13, 18,19,28	remove 5,9,19 because of missing event.
Canine Five	2/15/2005	26	2	FALSE	1	320	1.80	FALSE	70	35	30	641.4615	664.9615	608.7308	922.5769	768.4231	644.9615	0.0819	2	49.0385	11	-37.2615	-2.3000	-0.1292	5,7,9,15	**Not used:** Wrong PVC - 7,15 paced pre - 5,9 **Look at:** +2 missing: 8,27,28,29 +1 interesting: 17,23 Crazy base rate! Removed because paces in pre events.

SUBJECT		REPRODUCTION DETAILS										HRT averaged values						Turbulence Onset	SLOPE						NOTES	
Subject	Date	Numbers of files used	Channel Number Used Trims(1)	Negative Data Stream? Trims(2)	Pre-PVC blanking period Trims(3)	Post-PVC blanking period Trims(4)	Multiplication value for Std Dev of Threshold Trims(5)	Use of Inverse Data for the PVC? Trims(6)	Look for a PVC in each direction, when data & PVC is of opposite polarity Trim(7)	Duration to ignore peaks at the beginning of file Trim(8)	number of files Trim(9)	RR-2	RR-1	Coupling Interval	Compensatory Pause after VPB	RR1	RR2	Turbulence Onset	Max Slope Index	Max Slope	Min Slope Index	Min Slope	Median Slope	Mean Slope	Files that were removed	Additional Notes
		15	2	FALSE	1	320	1.80	FALSE	70	35	30	642.7333	677.9333	633.6667	859.8667	712.2000	620.0000	0.0087	1	57.9200	9	-49.1067	-1.0867	1.3236	5,7,8, 9, 12, 14, 15, 17, 21, 22, 23, 26-29	pace in pre: 5, 9, 12,14, 21,22,23,26 odd morph (+2) - 8, 29 wrong pvc - 7,15 missing +1: 17
Canine Five	3/8/2005	29	2	FALSE	80	250	2.50	TRUE	70	25	30	764.8276	755.7241	789.5517	608.4828	827.9655	786.6897	0.0619	3	28.7828	15	-36.1379	-6.8172	-2.6575	pvc16	Data incorrect because alignment of PVC is incorrect
		27	2	FALSE	10	250	2.50	TRUE	150	25	30	767.6667	746.6667	575.0000	833.9630	781.5185	761.0000	0.0186	3	25.1481	15	-31.2333	0.9444	-1.1842	16,17,25	Baseline fluctuation is high. Results lack HRT maybe due to baseline fluctuation and big spacing between first few events post PVC. 4 - spacing general 7,8 - big space 2+ - 3+ 25 - pace in pre evts 17 - event between 1+ and 2+? 19 - big space 1+ - 2+
Canine Five	3/29/2005	10	2	FALSE	230	300	1.80	TRUE	70	35	30	690.0000	871.7500	985.5000	730.0000	885.8750	768.3750	0.0592	2	67.4125	9	-33.3750	-10.0750	6.0392	3,5,8,12, 14-30	PVC hard to detect in most channels. Baseline noise existed for pvc1 to 17. **Wrong pvc:** 17, 24,27,26,29,30 **Missing Pre:** 12,14,15,16,19-23, 25, 28 **Missed Pre:** 18 **Missed Post:** 3 look at 5: little event at +1 **Removed because not ideal trims. Next more accurate.**
		17	2	FALSE	10	300	3.90	TRUE	200	35	30	661.5714	851.0000	789.6429	922.9286	1083.5000	941.8571	0.3390	3	101.4786	6	-52.5214	-1.1429	-9.6643	5,8,12, 17, 18,19, 22, 24-27,29,30	5,8,12,18 - noise make it impossible to tell if there is skipped beats 19,22 - extra paced evt 25 - missing pre 26,30 - where's PVC? 17,24,27,29 - wrong PVC GENERAL: Lots of noise. Base rate is all over the place. HRT not present.
Canine Five	3/29/2005	22	2	TRUE	10	300	2.90	TRUE	70	35	30	637.4000	635.6500	413.8500	826.5500	558.0000	592.9500	-0.0959	1	18.7600	14	-1.4600	0.3350	2.0083	4,6,8,10, 20,22,24, 25	Explant 20 - algo missed r-wave 6,10,22,24,25 - missing beat after pvc extra pace - 4,8 Note: 1,3 have extra paced events, used because more than 16 event prior to PVC